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RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
38TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE
Oxygenation in the Critically Ill Patient
Part II

- Oxygen Toxicity in the Critically Ill Patient
- Pharmacologic Approaches to Respiratory Failure
- Therapeutic Manipulation of Oxygen Consumption and Carbon Dioxide Production in Acute Respiratory Failure
- A Mechanistic Approach To Providing Adequate Oxygenation in Acute Hypoxemic Respiratory Failure
- Oxygen Transport: Does Increasing Supply Improve Outcome?
- Cost-Benefit Considerations in Managing Oxygenation Failure
- Conference Summary

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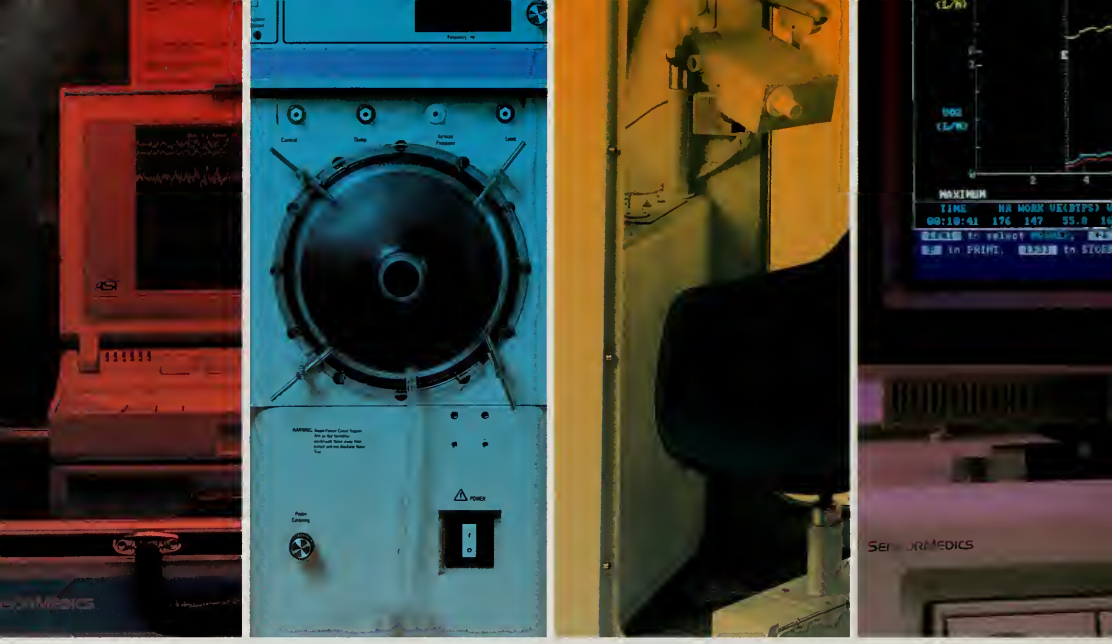

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David J. Pierson, MD and Leonard D. Hudson, MD

July 29, 1993: 12:30 p.m. to 2p.m. EST

Pulmonary Function Testing — When, Why, and What?

David J. Pierson, MD, and Charles G. Irvin, PhD

September 30, 1993: 12:30p.m. to 2 p.m. EST

Unconventional Methods for Adult Oxygenation and Ventilation Support

David J. Pierson, MD, and James K Stoller, MD

December 2, 1993: 12:30 p.m. to 2 p.m. EST

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in Puerto Vallarta, Mexico

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Chairmen and Guest Editors

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New Concepts in the Formation of Pulmonary Edema (editorial)—JD Crapo. Am Rev Respir Dis 1993;147:790-792. (Pertains to Bachofen et al papers abstracted on Pages 723 and 725.)

Recent Advances in Pulmonary Medicine: First of Two Parts (review)—SE Weinberger. N Engl J Med 1993;328(19):1389-1397.

Contribution of Rib Cage and Abdominal Movement to Ventilation for Successful Weaning from Mechanical Ventilation—R Ochiai, M Shimada, J Takeda, Y Iwao, K Fukushima. Acta Anaesthesiol Scand 1993;37:131.

In order to test the hypothesis whether the breathing pattern is helpful in predicting weaning outcome in patients being weaned from mechanical ventilation, 38 patients who underwent operation for esophageal cancer were evaluated at weaning from mechanical ventilation (19 unsuccessful weanings, Group U, and 19 successful weanings in age-matched patients, Group S). Since all patients initially fulfilled our weaning criteria, ventilatory parameters such as tidal volume, respiratory frequency, minute ventilation, and arterial blood gas analysis showed no significant differences between the groups. The breathing pattern was registered quantitatively by means of respiratory inductive plethysmography at 3 cm H_2O (0.3 kPa) of CPAP prior to weaning. The contribution of rib cage movement to tidal volume (%RC) was significantly greater in Group U than in Group S ($p < 0.05$). Indeed, 84% of the patients in Group S showed %RC less than 50%, compared to only 16% of the patients in Group U ($p < 0.05$). The results suggest that the breathing pattern is one important factor in predicting the outcome of weaning in patients after thoraco-abdominal surgery. Diaphragmatic fatigue is suspected to be the mechanism for the increase in the RC component in patients with unsuccessful weaning outcome.

Laser Bronchoscopy in Respiratory Failure from Malignant Airway Obstruction—IT Stanopoulos, JF Beamis Jr, FJ Martinez, K Vergos, SM Shapshay. Crit Care Med 1993;21(3):386.

OBJECTIVE: To examine the value of laser bronchoscopy in patients with inoperable carcinoma of the lung who required ventilatory assistance for acute respiratory failure. DESIGN: Retrospective review of the medical records of all patients undergoing laser bronchoscopy. SETTING: The Lahey Clinic Medical Center, a tertiary referral center. PATIENTS: The medical records of 311 patients undergoing laser bronchoscopy at the Lahey Clinic Medical Center between 1982 and 1990 were reviewed. The 17 patients who required mechanical ventilation at the time of laser surgery formed the study group. INTERVENTIONS: All patients underwent neodymium: yttrium-aluminum-garnet laser bronchoscopy through a rigid bronchoscope in the operating room with use of jet ventilation and general anesthesia throughout the procedure. Postoperative care was directed by the same physician for all patients. MEASUREMENTS & MAIN RESULTS: The following data were extracted from medical records: age and sex of patient, cell type and location of tumor, length of time between diagnosis and laser therapy, treatment before and after laser therapy, number of days receiving mechanical

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INDICATIONS AND USAGE

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Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	SURVANTA (%)	Control (%)	P-Value[a]
Patent ductus arteriosus	46.9	47.1	0.614
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.629
Pulmonary air leaks	10.8	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	5.1	5.3	0.427
Apnea	65.4	59.6	0.263
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a]P-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P = 0.001$; and 48.8% *v* 34.2%, $P = 0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardiorespiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

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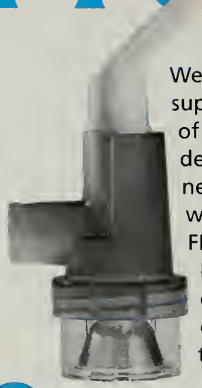

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ventilation before and after laser therapy, medical and operative complications, survival, and cause of death. The patients were divided into two groups on the basis of clinical improvement that permitted elective discontinuation of mechanical ventilation. Group 1 included patients who experienced clinical improvement permitting endotracheal extubation. Group 2 was composed of patients who died while still receiving mechanical ventilatory support or who were extubated before institution of comfort measures. The two groups were compared using nonparametric tests of significance, including the Mann-Whitney test. No significant differences were apparent between Groups 1 and 2 regarding clinical characteristics before laser treatment. Patients in Group 1 had significantly ($p = 0.03$) shorter requirements for mechanical ventilation after laser treatment than patients in Group 2 (1 vs 6 days). Similarly, patients in Group 1 were more likely to receive additional treatment after laser therapy than patients in Group 2 (seven of nine patients vs two of eight patients; $p = 0.048$). Patients in Group 1 had significantly ($p = 0.0038$) longer survival than patients in Group 2 (98 vs 8.5 days). A greater endobronchial component to airway obstruction appeared to exist in patients in Group 1 (nine of nine patients) vs patients in Group 2 (three of eight patients; $p = 0.009$). Extrinsic compression and submucosal tumor were more commonly seen in patients in Group 2. In addition, patients in Group 2 appeared to have a greater number of postoperative medical complications than patients in Group 1. Operative complications were minor in both groups. CONCLUSIONS: In nine of 17 patients, laser bronchoscopy appeared to improve the clinical status, permitting removal of mechanical ventilation and extubation and provided the opportunity for further treatment modalities in seven of the nine patients. Survival was improved in this subgroup, and requirement for mechanical ventilatory support was shortened. The improved outcome after laser therapy was related to the presence of obstructing endobronchial tumor as the cause of the respiratory insufficiency. Patients with inoperable carcinoma of the lung and respiratory failure should be evaluated for the presence of an endobronchial lesion that might be responsive to laser bronchoscopy.

Nosocomial Pneumonia in Ventilated Patients: A Cohort Study Evaluating Attributable Mortality and Hospital Stay—J-Y Fagon, J Chastre, AJ Hance, P Montravers, A Novara, C Gibert. Am J Med 1993; 94:281.

PURPOSE: Although nosocomial pneumonia is a common problem in intubated and ventilated patients, previous studies have not clearly demonstrated that nosocomial pneumonia actually results in increased mortality or prolongs hospitalization of these patients. In an attempt to answer these questions, we have performed a cohort study in which patients who developed nosocomial pneumonia and control subjects were carefully matched for the severity of underlying illness and other important variables. PATIENTS & METHODS: Case patients were 48 ventilated patients with nosocomial pneumonia identified on the basis of results of protected specimen brush quantitative culture and identification of intracellular organisms in cells recovered by bronchoalveolar lavage. For matching cases and their respective controls, the following variables were used: age (± 5 years), Simplified Acute Physiologic Score (± 3 points), indication for ventilatory support, date of admission, and duration of exposure to risk. RESULTS: Successful matching was achieved for 222 of 240 (92.5%) variables. The mortality rate in cases was 26 of 48 (54.2%) compared with 13 of 48 (27.1%) in controls. The attributable mortality was 27.1% (95% confidence interval [CI], 8.3% to 45.9%; $p < 0.01$) and the risk ratio for death was 2.0 (95% CI, 1.61 to 2.49). The mean length of stay was 34 days for cases and 21 days for controls ($p < 0.02$). In the case of pneumonia due to Pseudomonas or *Acinetobacter* species, the mortality rate was 71.4%, the attributable mortality was 42.8% (95% CI, 14.5% to 69.0%), and the risk ratio was 2.50 (95% CI, 1.31 to 4.61). CONCLUSION: Pneumonias occurring in ventilated patients, especially those due to *Pseudomonas* or *Acinetobacter* species, are associated with considerable mortality in excess of that resulting from the underlying disease alone, and significantly prolong the length of stay in the intensive care unit.

Risk of Human Immunodeficiency Virus Infection among Emergency Department Workers—R Marcus, DH Culver, DM Bell, PU Srivastava, MH Mendelson, RJ Zalenski, et al. Am J Med 1993;94:363.

PURPOSE: To estimate (1) the prevalence of human immunodeficiency virus (HIV) infection in emergency department (ED) patients, (2) the frequency of blood contact (BC) in ED workers (EDWs), (3) the efficacy of gloves in preventing BC, and (4) the risk of HIV infection in EDWs due to BC. PATIENTS & METHODS: We conducted an 8-month study in three pairs of inner-city and suburban hospital EDs in high AIDS incidence areas in the United States. At each hospital, blood specimens from approximately 3,400 ED patients were tested for HIV antibody. Observers monitored BC and glove use

by EDWs. RESULTS: HIV seroprevalence was 4.1 to 8.9 per 100 patient visits in the 3 inner-city EDs, 6.1 in 1 suburban ED, and 0.2 and 0.7 in the other 2 suburban EDs. The HIV infection status of 69% of the infected patients was unknown to ED staff. Seroprevalence rates were highest among patients aged 15 to 44 years, males, blacks and Hispanics, and patients with pneumonia. BC was observed in 379 (3.9%) of 9,793 procedures: 362 (95%) of the BCs were on skin, 11 (3%) were on mucous membranes, and 6 (2%) were percutaneous. Overall procedure-adjusted skin BC rates were 11.2 BCs per 100 procedures for ungloved workers and 1.3 for gloved EDWs (relative risk = 8.8; 95% confidence interval = 7.3 to 10.3). In the high HIV seroprevalence EDs studied, 1 in every 40 full-time ED physicians or nurses can expect an HIV-positive percutaneous BC annually; in the low HIV seroprevalence EDs studied, 1 in every 575. The annual occupational risk of HIV infection for an individual ED physician or nurse from performing procedures observed in this study is estimated as 0.008% to 0.026% (1 in 13,100 to 1 in 3,800) in a high HIV seroprevalence area and 0.0005% to 0.002% (1 in 187,000 to 1 in 55,000) in a low HIV seroprevalence area. CONCLUSIONS: In both inner-city and suburban EDs, patient HIV seroprevalence varies with patient demographics and clinical presentation; the infection status of most HIV-positive patients is unknown to ED staff. The risk to an EDW of occupationally acquiring HIV infection varies by ED location and the nature and frequency of BC; this risk can be reduced by adherence to Universal Precautions.

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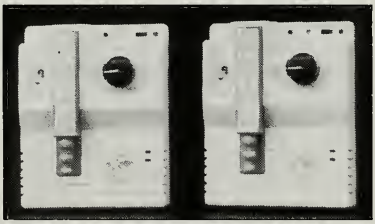

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Efficacy of Pressure Support in Compensating for Apparatus Work—AD Bersten, AJ Rutten, AE Vedig. Anaesth Intens Care 1993; 21:67.

Breathing through an endotracheal tube, connector, and ventilator demand valve imposes an added load on the respiratory muscles. As respiratory muscle fatigue is thought to be a frequent cause of ventilator dependence, we sought to examine the efficacy of five different ventilators in reducing this imposed work through the application of pressure support ventilation. Using a model of spontaneous breathing, we examined the apparatus work imposed by the Servo 900C, Puritan-Bennett 7200a, Engstrom Erica, Dräger EV-A or Hamilton Veolar ventilators, a size 7.0- and 8.0-mm endotracheal tube, and inspiratory flowrates of 40 and 60 L/min. Pressure support of 0, 5, 10, 15, 20, and 30 cm H_2O was tested at each experimental condition. Apparatus work was greater with increased inspiratory flowrate and decreased endotracheal tube size, and was lowest for the Servo 900C and Puritan-Bennett 7200a ventilators. Apparatus work fell in a curvilinear fashion when pressure support was applied, with no major difference noted between the five ventilators tested. At an inspiratory flowrate of 40 L/min, a pressure support of 5 and 8 cm H_2O compensated for apparatus

work through size 8.0 and 7.0 endotracheal tubes and the Servo 900C and Puritan-Bennett 7200a ventilators. However, the maximum negative pressure was greater for the Servo 900C. The added work of breathing through endotracheal tubes and ventilator demand valves may be compensated for by the application of pressure support. The level of pressure support required depends on inspiratory flowrate, endotracheal tube size, and type of ventilator.

Influence of Sensor Site Location on Pulse Oximetry Kinetics in Children—LM Reynolds, SC Nicolson, JM Steven, A Escobar, ME McGonigle, DR Jobes. Anesth Analg 1993;76:751.

A pulse oximeter sensor is used to monitor changes in arterial hemoglobin oxygen saturation (S_{pO_2}) in anesthetized pediatric patients. The authors compared the kinetics of desaturation and resaturation measured by sensors placed over central (tongue, cheek) and peripheral (finger, toe) vascular beds in children with congenital heart disease. Desaturation time was defined as the time that elapsed between the onset of apnea and a 4% decrease in S_{pO_2} from baseline. The desaturation times averaged 24 ± 12 s, 56 ± 34 s, and 58 ± 28 s for the cheek, finger, and toe, respectively ($n = 40$; $p < 0.0001$ for cheek versus finger or toe). Resaturation time was defined as the interval between the resumption of ventilation and a 4% increase in S_{pO_2} above the nadir. Resaturation times averaged 12 ± 8 s for the cheek, 40 ± 36 s for the finger, and 47 ± 25 s for the toe ($n = 40$; $p < 0.0001$ for cheek versus finger or toe). A comparison of the kinetics at two central sensor sites, cheek and tongue, respectively, revealed no significant differences in desaturation times (20 ± 10 s vs 21 ± 9 s) or resaturation times (10 ± 6 s vs 7 ± 3 s) ($n = 13$). The authors conclude that both desaturation and resaturation are detected earlier by centrally placed sensors.

Acute Mountain Sickness in a General Tourist Population at Moderate Altitudes—B Honigman, MK Theis, J Koziol-McLain, R Roach, R Yip, C Houston, LG Moore. Ann Intern Med 1993;118:587.

OBJECTIVE: To determine the incidence of acute mountain sickness in a general population of visitors to moderate elevations, the characteristics associated with it, and its effect on physical activity. DESIGN: A cross-sectional study. SETTING: Resort communities located at 6,300 to 9,700 feet elevation in the Rocky Mountains of Colorado. PARTICIPANTS: Convenience sample of 3,158 adult travelers, 16 to 87 years old (mean age [± SD], 43.8 ± 11.8 years). RESULTS: 25% of the travelers to moderate elevations developed acute mountain sickness, which occurred in 65% of travelers within the first 12 hours of arrival. Fifty-six percent of those with symptoms reduced their physical activity. The odds favoring acute mountain sickness were 3.5 times as large for visitors whose permanent residence was below 3,000 feet elevation as for those whose residence was above 3,000 feet; 2.8 times as large for visitors with previous symptoms of acute mountain sickness; and twice as large in travelers younger than 60 years. Women, obese persons, those in poor or average physical condition, and those with underlying lung disease also had a higher occurrence of acute mountain sickness ($p < 0.05$). CONCLUSIONS: Acute mountain sickness occurs in 25% of visitors to moderate altitudes and affects activity in most symptomatic visitors. Persons who are younger, less physically fit, live at sea level, have a history of acute mountain sickness, or have underlying lung problems more often develop these symptoms.

Lung Function and Surfactant Distribution in Saline-Lavaged Sheep Given Instilled vs Nebulized Surfactant—JF Lewis, B Tabor, M Ikegami, AH Jobe, M Joseph, D Absolom. J Appl Physiol 1993;74(3):1256.

Adult sheep (35 ± 3 kg) underwent saline lung lavage and 1.5 h of mechanical ventilation to induce acute lung injury. Animals received 100 mg lipid/kg body wt of tracheally instilled surfactant (Inst Surf) or either nebulized surfactant (Neb Surf) or nebulized saline (Neb Saline) and were killed 3 h later. Inst Surf and Neb Surf groups had significant improvements in oxygenation ($p < 0.01$) and peak inspiratory pressures (PIP) ($p < 0.05$) compared with pretreatment values. Improvements in oxygenation and PIP for Inst Surf animals were significantly greater than for Neb Surf animals ($p < 0.05$). Volumes of maximal pressure of quasi-static pressure-volume curves measured at the time the animals were killed were significantly greater for Inst Surf and Neb Surf animals than for animals given Neb Saline ($p < 0.05$). Alveolar recovery of exogenous surfactant was 100 times greater for Inst Surf animals (1.732 ± 70 mg) than for Neb Surf animals (15.3 ± 2.9 mg) at the time they were killed. Although there were no differences in exogenous surfactant distribution patterns at the lobar level between the two surfactant-treated groups, distribution histograms calculated for 10-g lung pieces revealed the Neb Surf animals had significantly more pieces within 25% of the mean value of 1.0 (42.7 ± 6.9%) than did Inst Surf animals (20.8 ± 5.5%)

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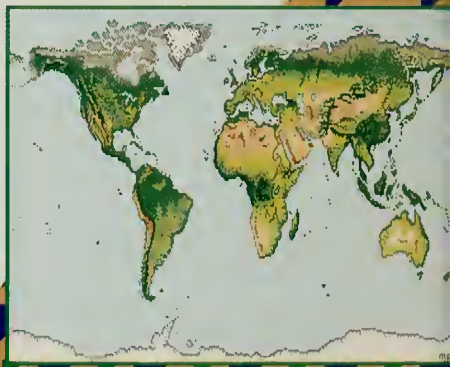

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($p < 0.01$). Exogenous surfactant therapy improved lung function with significantly different quantities of surfactant deposited in lung tissue for the two delivery methods evaluated.

Validity of the Esophageal Balloon Technique at High Frequencies—R Peslin, D Navajas, M Rotger, R Farré. J Appl Physiol 1993;74(3): 1039.

The reliability of the esophageal balloon technique in measuring high-frequency changes in pleural pressure (P_{pl}) was investigated in six normal subjects by studying the amplitude ratio (A) and phase angle (Φ) of esophageal (P_{es}) and mouth (P_m) pressures during airway occlusion and while pseudorandom pressure variations (2-32 Hz) were applied to the chest. The measurements were made with a common esophageal balloon-catheter system connected to a high-impedance piezoresistive transducer. When the cheeks were firmly supported, *A* averaged 1.08 ± 0.063 at 2 Hz and 1.06 ± 0.11 at 32 Hz. P_{es} increasingly led P_m with increasing frequency, and Φ averaged 20.8 ± 4.0° at 32 Hz. Washing the airways with 80% He-20% O_2 reduced Φ by 50%. When the cheeks were not supported, *A* exhibited a strong positive frequency dependence, averaging 1.71 ± 0.34 at 32 Hz, whereas Φ increased much faster below 20 Hz and tended to decrease afterward. Because the esophageal transfer function $P_{es}/P_{pl} = (P_{es}/P_m)/(P_{pl}/P_m)$, we could estimate P_{es}/P_{pl} by computing for individual subjects the pressure difference between the pleura and the mouth based on the lung and upper airway wall properties that were measured separately. The results suggest that the ratio of P_{es} and P_{pl} remains close to unity from 2 to 32 Hz, but P_{es} lags slightly behind P_{pl} (Φ equals about –7° at 32 Hz).

Inhaled Nitric Oxide Reverses Hypoxic Pulmonary Vasoconstriction without Impairing Gas Exchange—U Pison, FA López, CF Heidelmeyer, R Rossaint, KJ Falke. J Appl Physiol 1993;74(3):1287.

Nitric oxide (NO) is an endogenous endothelium-derived relaxing factor that participates in the regulation of vascular tone. We studied the effects of inhaled NO gas on transient hypoxic pulmonary vasoconstriction and normal lungs in mechanically ventilated sheep. We measured hemodynamics and pulmonary gas exchange. For gas exchange measurements we used conventional blood gas analysis and the multiple inert gas elimination technique to estimate ventilation-perfusion heterogeneity. Our hypotheses were (1) inhaled NO reverses hypoxic pulmonary vasoconstriction, (2) the hemodynamic effects of inhaled NO are limited to the pulmonary circulation, and (3) inhaled NO does not impair pulmonary gas exchange and may redistribute blood flow to better ventilated areas of the lungs. Hypoxic pulmonary vasoconstriction was induced by using a hypoxic inspiratory gas mixture. The addition of 20 ppm NO to the hypoxic inspiratory gases returned pulmonary arterial pressure to baseline values. Systemic hemodynamics and gas exchange indexes derived from conventional blood gas analysis remained constant. Gas exchange indexes for ventilation-perfusion ratios and gas dispersions improved. The addition of 20 ppm NO to medical air (21% O_2) had no such significant effects on hemodynamics or pulmonary gas exchange. Our findings show that inhaled NO reverses transient hypoxic pulmonary vasoconstriction. The hemodynamic effects of NO are limited to the pulmonary circulation; it does not impair pulmonary gas exchange. Moreover, it redistributes blood flow to better ventilated alveoli. As such, NO has potential in the treatment of lung diseases associated with pulmonary hypertension.

Transmission of HIV-Associated Tuberculosis to Healthcare Workers—G Di Perri, G-P Cadeo, F Castelli, R Micciolo, S Bassetti, F Rubini, et al. Infect Control Hosp Epidemiol 1993;14:67.

OBJECTIVE: A retrospective investigation was made to compare the occupational risk of tuberculosis in personnel assisting human immunodeficiency virus (HIV)-infected and uninfected subjects with active tuberculosis. DESIGN: We retrospectively reviewed 6 years of hospital activity in 3 units where HIV-infected patients with tuberculosis are hospitalized and in 2 units where non-HIV-infected tuberculosis patients are hospitalized. The risk of occupational tuberculosis in healthcare workers who assisted HIV-infected and non-HIV-infected patients with tuberculosis was investigated. PARTICIPANTS: The risk of occupational tuberculosis in healthcare workers was studied by considering the numbers of potential source cases (hospitalized patients with tuberculosis) in the two conditions investigated (HIV-positive and HIV-negative). Both potential source cases and cases of tuberculosis in healthcare workers had to be microbiologically proven in order to be considered. RESULTS: Seven cases of tuberculosis occurred in persons who cared for 85 HIV-infected subjects with tuberculosis, while only 2 cases occurred in staff members who took care of 1,079 HIV-negative tuberculosis patients over the same period (relative risk = 44.4; 95% confidence interval = 8.5-438). CONCLUSIONS: Tuberculosis seems no longer to be a neglectable risk in healthcare workers assisting patients with HIV infection. Further study is urgently needed to see whether such

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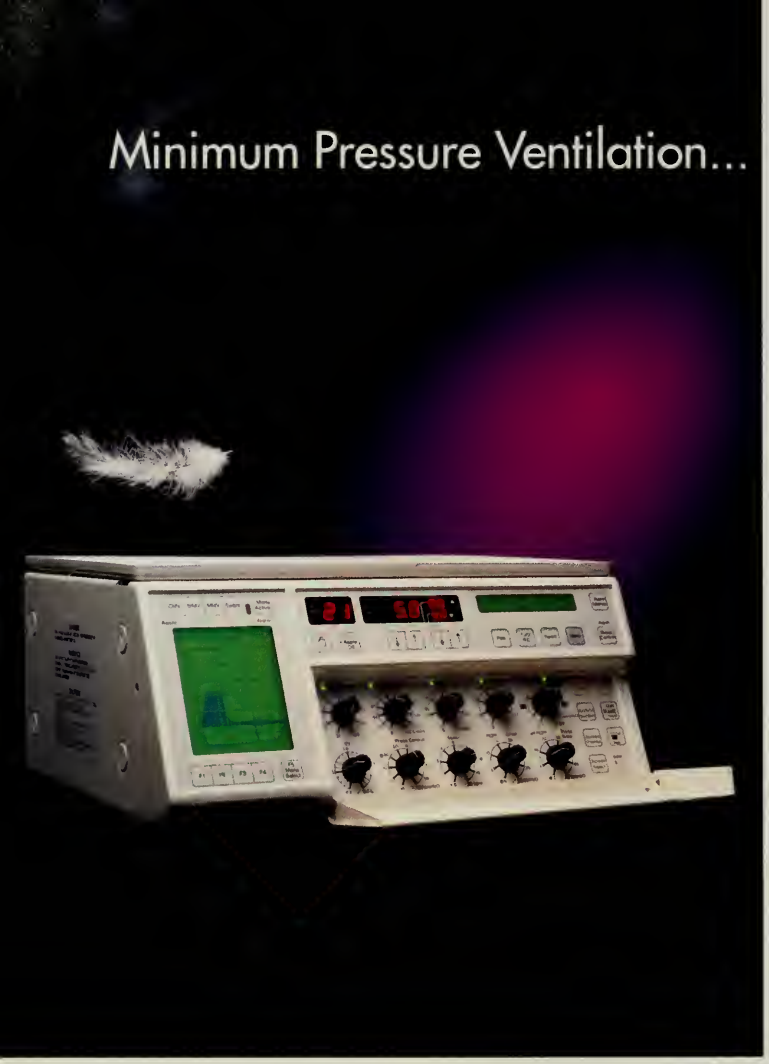

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unexpectedly high dissemination of tuberculosis also is demonstrable in the community.

Long-Term Pulmonary Consequences of Respiratory Distress Syndrome in Preterm Infants Treated with Exogenous Surfactant—S Abbasi, VK Bhutani, JS Gerdes. J Pediatr 1993;122:446.

The pulmonary outcome for preterm infants 1 year after synthetic surfactant replacement for respiratory distress syndrome was assessed by examining their pulmonary status and the results of pulmonary function tests. A total of 47 infants were followed: 13 infants (mean ± SD birthweight, 1,960 ± 616 gm; gestation, 32 ± 1.1 weeks) had been assigned to the placebo group and 34 (birthweight = 1,890 ± 530 gm; gestation = 32 ± 2.5 weeks) to surfactant treatment. The infants were examined at 3 to 6 months of age (n = 45) and at 9 to 12 months of age (n = 36). There were no significant differences between the two groups in predisposing clinical conditions that would lead to chronic lung disease. The infants had similar patterns of growth, respiratory-related illness, and need for theophylline therapy, diuretic therapy, or both. None had hypoxemia by pulse oximetry. Mean (± SEM) values for pulmonary mechanics and energetics in surfactant-treated infants were significantly ($p < 0.01$) lower for total pulmonary resistance in late infancy (57.7 ± 11.7 vs 35.3 ± 4.6 cm H_2O/L/s). Lower values (mean ± SEM) of resistive work of breathing were also measured in the surfactant-treated group (60.7 ± 12.0 vs 38.2 ± 3.6 gm-cm/kg per breath). The dynamic pulmonary compliance values were in the low-normal range for both groups, and the mean (± SEM) peak-to-peak esophageal pressure values were elevated (11.47 ± 2.26 cm H_2O in the placebo group; 9.24 ± 0.69 cm H_2O in the surfactant group). Forced expiratory flow measurements in late infancy demonstrated significant ($p < 0.01$) improvement in expiratory reserves and reduced evidence of airflow obstruction in the surfactant-treated infants (peak flow [mean ± SEM]: 287.1 ± 69 vs 396.9 ± 27 mL/s; forced expiratory flow [mean ± SEM] at functional residual capacity: 56.3 ± 7.5 vs 83.4 ± 19.5 mL/s). No significant differences in pulmonary functions were noted in early infancy. These data suggest that surfactant replacement for respiratory distress syndrome may be associated with beneficial long-term effects on the resistive airflow properties of larger preterm infants.

Saturation by Pulse Oximetry: Comparison of the Results Obtained by Instruments of Different Brands—EH Thilo, D Andersen, ML Wasserstein, J Schmidt, D Luckey. J Pediatr 1993;122:620.

We noticed that arterial oxygen saturation by pulse oximetry (S_{pO_2}) was generally lower when determined by the Ohmeda Biox 3700 pulse oximeter than when determined by the Nellcor N-100 pulse oximeter, and we investigated whether this finding was consistent and the reason for the discrepancy. We placed both oximeters simultaneously on 30 infants with indwelling arterial catheters and measured arterial partial pressure of oxygen (P_{aO_2}), percentage of fetal hemoglobin, and complete CO-oximetry, including arterial oxygen saturation (S_{aO_2}) with a Radiometer OSM-3 CO-oximeter, with and without correction for fetal hemoglobin levels, in four samples of blood from each infant during a 12-hour period for a total of 120 samples. The Nellcor S_{pO_2} was consistently higher than the Ohmeda S_{pO_2} by a mean (± SD) of 1.61% ± 2.69% ($p < 0.001$). The Nellcor S_{pO_2} correlated best with functional S_{aO_2} [oxyhemoglobin (H_{bO_2}) /(H_{bO_2} + reduced hemoglobin) × 100]; Ohmeda S_{pO_2} correlated best with fractional S_{aO_2} [H_{bO_2}/(H_{bO_2} + reduced hemoglobin + carboxyhemoglobin + methemoglobin) × 100], reflecting a fundamental difference in the calibration algorithms used in the two instruments. A desired P_{aO_2} of 50 to 100 mm Hg, is maintained when the range of S_{pO_2} is 90% to 96% for Ohmeda S_{pO_2} and 92% to 98% for Nellcor S_{pO_2} in the neonate, giving a positive predictive value in this study of 94% to 95%. We conclude that S_{pO_2} determined by pulse oximeters of different brands is not interchangeable, and this may be of clinical importance in predicting P_{aO_2} on the basis of S_{pO_2}.

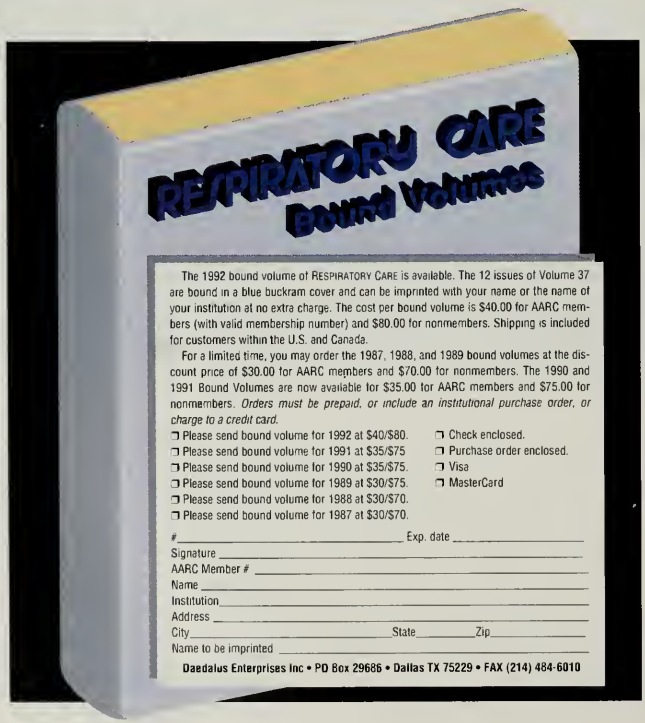
Experimental Hydrostatic Pulmonary Edema in Rabbit Lungs: Morphology—H Bachofen, S Schürch, RP Michel, ER Weibel. Am Rev Respir Dis 1993;147:989.

To study the accumulation and distribution of edema fluid and the associated changes in alveolar microarchitecture, edema was induced in excised rabbit lungs perfused with a 6% albumin solution. The lungs, including the edema fluid, were then fixed by vascular perfusion with glutaraldehyde, osmium tetroxide, and uranyl acetate. Tissue samples were analyzed by light microscopy and transmission and scanning electron microscopy. We found (1) fixation was successful in that the albumin in the edema fluid formed coherent webs indicating the location and arrangement of the extravascular fluid accumulations; (2) regardless of the filtration pressure (about 29 mm Hg in one set of experiments and about 14 mm Hg in the other), an apical-to-basal gradient of fluid accumulation was found. This gradient was absent in lungs held in the inverse position, suggesting that the re-

gional distribution of pulmonary edema is not simply gravity dependent. At the same lung height, there was a remarkable inhomogeneity of interstitial and alveolar edema. (3) Both the inhomogeneous distribution of fluid and the resulting changes in surface tension affected the entire alveolar architecture. (4) Within interstitial and alveolar spaces, there were striking inequalities in the density of the proteinaceous fluid pools that suggest local differences in the sieving properties of the barriers, that is, in the reflection coefficients for albumin. In conclusion, our findings suggest that the formation of pulmonary edema cannot be explained solely by uniform membrane models for fluid exchange.

Randomized Study of High-Frequency Oscillatory Ventilation in Infants with Severe Respiratory Distress Syndrome—HiFO Study Group. J Pediatr 1993;122:609.

We conducted a multicenter, prospective, noncrossover, randomized study to determine whether high-frequency oscillatory ventilation (HFOV) would decrease the development or progression of air leak syndrome in infants with severe respiratory distress syndrome. Air leak syndrome was defined as pulmonary interstitial emphysema or gross air leak such as pneumothorax. Infants were eligible for study entry if they were less than 48 hours of age and had severe respiratory distress syndrome, defined by peak inspiratory pressure or the presence of air leak syndrome. Infants who weighed ≥ 0.5 kg at birth were randomly assigned to receive either conventional ventilation (CV) or HFOV. HFOV was provided by a ventilator that operated at 15 Hz, with a 1:2 inspiratory-expiratory ratio and no background tidal breaths. Severity of pulmonary interstitial emphysema was scored independently by two neonatologists unaware of the infants' ventilatory group. Gross air leak severity was scored according to the number of chest tubes required and duration of air leak. Eight-six infants received HFOV; 90 received CV. During the first 24 hours of the study, patients in the HFOV group received significantly higher mean airway pressure and lower inspired oxygen concentration, had significantly lower arterial carbon dioxide tension, and had a higher ratio of arterial-to-alveolar oxygen tension. When the HFOV and CV groups were compared with control for birthweight strata, study site, and inborn versus outborn status, HFOV significantly reduced the development of air leak syndrome in those patients who entered the study without the syndrome. We conclude that HFOV, when the strategy employed in this study is used, provides effective ventilation, improves oxygenation, and significantly reduces the development of air leak syndrome in infants with severe respiratory distress syndrome.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Lung Function, Pre- and Postnatal Smoke Exposure, and Wheezing in the First Year of Life—IB Tager, JP Hanrahan, TD Tosteson, RG Castile, RW Brown, ST Weiss, FE Speizer. Am Rev Respir Dis 1993;147:811.

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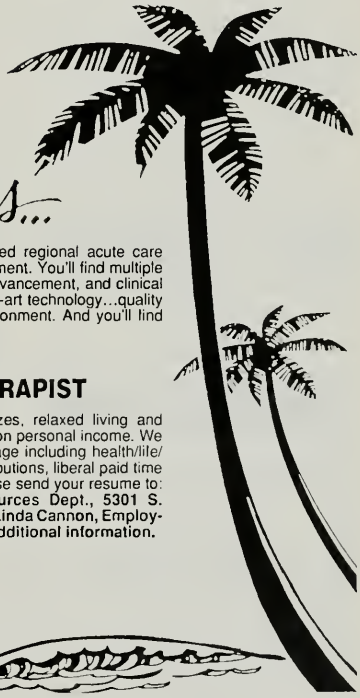

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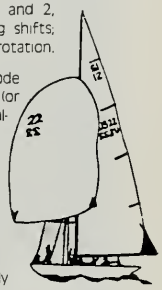

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(LRI) was studied in 97 infants in whom the first measurement of pulmonary function (PFT) was made before 6 months of age. Occurrence of LRI was evaluated by standardized questionnaires at each well-baby visit, biweekly telephone calls to mothers, and review of all visits to physicians. Infant PFT was assessed by partial expiratory flow-volume curves and helium-dilution measurement of functional residual capacity (FRC). Maternal, prenatal smoking was assessed by urine cotinine and standard questionnaires. Infants who developed an LRI during the first year of life had lower pre-illness length-corrected forced expiratory flow at FRC (V_{FRC}) than those who did not experience an LRI (males, 2.06 ± 0.20 versus 2.32 ± 0.29 mL/s/cm; females, 238 ± 0.20 versus 2.91 ± 0.26 mL/s/cm). Similar results were observed with FRC-corrected V_{FRC}. No differences were observed for FRC. Differences in lung function were greatest in female infants whose mothers did not smoke during pregnancy (V_{FRC} 2.67 ± 0.25 versus 3.49 ± 0.26 mL/s/cm for those with and without LRI, respectively; $p = 0.03$). History of maternal wheezing was more common in infants who experience an LRI, independent of maternal smoking. The results were not influenced by exposure to non-maternal sources of environmental tobacco smoke in the postnatal period. Regression analyses that included data for multiple measurements of V_{FRC} over the first year and took account of duration of follow-up demonstrated that lower levels of V_{FRC} were associated with an increased frequency of LRI, especially in female infants. The results indicate that pre-existing abnormalities of respiratory function associated with *in utero* exposure to tobacco smoke products and familial predisposition to wheezing are important determinants of wheezing LRI in the first year of life.

Particulate Air Pollution and Hospital Emergency Room Visits for Asthma in Seattle—J Schwartz, D Slater, TV Larson, WE Pierson, JQ Koenig. Am Rev Respir Dis 1993; 147:826.

Recent studies have associated short-term exposure to respirable particulate matter (PM_{10}) exposure with peak flow decrements, increased symptoms of respiratory irritation, increased use of asthma medications, and increased hospitalization for asthma. Increased mortality from chronic respiratory disease has also been reported. To help confirm whether PM_{10} exposure is a risk factor for the exacerbation of asthma, we compiled daily records of asthma emergency room visits from eight hospitals in the Seattle area. In Poisson regressions controlling for weather, season, time trends, age, hospital, and day of the week, the daily counts of emergency room visits for persons under age 65 were significantly associated with PM_{10} exposure on the previous day. The mean of the previous 4 days' PM_{10} was a better predictor ($p < 0.005$). The relative risk for a 30 $\mu g/m^3$ increase in PM_{10} was 1.12 (95% confidence interval 1.20 to 1.04). Daily PM_{10} concentrations never exceeded 70% of the current ambient air quality standards during the period. The consistency of investigations of the health effects of PM_{10} suggest that increased attention should be given to the control of particulate matter air pollution.

Experimental Hydrostatic Pulmonary Edema in Rabbit Lungs: Barrier Lesions—H Bachofen, S Schürch, ER Weibel. Am Rev Respir Dis 1993;147:997.

In excised rabbit lungs perfused with a 6% albumin solution, hydrostatic pulmonary edema was induced by moderate (about 14 mm Hg) and high increases (about 29 mm Hg) of capillary transmural pressure. Thereafter, lung tissue and proteinaceous edema fluid were fixed by vascular perfusion and analyzed by electron microscopy for possible lesions of the blood-gas barrier. The following observations appear noteworthy: (1) There were distinct and numerous lesions of the epithelial cell layer. In high-pressure edema, frank disruptions on the thin and thick sides of the blood-gas barrier were prominent. In moderate-pressure edema epithelial blebs were more conspicuous. (2) In contrast, endothelial lesions were rare in both high- and moderate-pressure experiments. (3) Epithelial Type-I cells revealed an enormous plasticity as illustrated by the formation of large epithelial blebs. (4) Although the entire microvasculature was subjected to high pressures, barrier lesions were exclusively seen in regions with alveolar edema. These findings suggest that barrier leaks play a role in both hydrostatic and permeability lung edema and that the differences between both types of edema rather reflects the type and extent of injury to the alveolar epithelial barrier and the associated inflammatory reaction.

Unrecognized Pertussis Infection in Adolescents—BA Cromer, J Goydos, J Hackell, J Mezzatesta, C Dekker, EA Mortimer. AJDC 1993;147: 575.

Little information is available regarding the level of immunity to *Bordetella pertussis* among adolescents. We measured serum antibodies in 156 healthy adolescents to the following pertussis antigens: pertussis toxin, filamentous hemagglutinin, and 69-kd outer membrane protein. In an attempt to identify intercurrent pertussis infections, we also obtained a total of 43 repeated samples during the following 5 years. Using a 50% or greater rise in IgG enzyme-linked

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immunosorbent assay titers to define seroconversion, we found an annual incidence of 6.1%; by alternative definitions of seropositivity, the predicted annual incidence of infection ranged from 1.2% to 8.2%. These data suggest that infection with *B pertussis* is common in the adolescent population.

The Impact on Infant Birth Weight and Gestational Age of Cotinine-Validated Smoking Reduction during Pregnancy—CQ Li, RA Windsor, L Perkins, RL Goldenberg, JB Lowe. JAMA 1993;269: 1519.

OBJECTIVE: To evaluate the impact of cotinine-confirmed smoking reduction during pregnancy on infant birth weight and gestational age at birth. DESIGN: Group analyses from a prospective, randomized smoking-cessation intervention trial using cotinine levels to assess smoking cessation and reduction. SETTING: Four maternity clinics of Jefferson County Health Department in Birmingham, AL. PATIENTS: A total of 803 pregnant smokers and 474 never smokers with a fetal gestational age of 32 weeks or less at the first prenatal visit to a clinic. MAIN OUTCOME MEASURES: Infant birth weight and gestational age at birth. RESULTS: Infants who were born to women who quit smoking (quitters) had the highest mean birth weight (3,371 ± 581 g), followed by infants who were born to women who reduced smoking (reducers) (3,120 ± 651 g), and infants who were born to women who did not change smoking behavior (no changers) (3,043 ± 587 g). The mean infant birth weight of infants born to the quitters, adjusted by mother's age, race, height, weight at baseline, and gestational age at delivery was 241 g heavier than that among the no changers ($p = 0.0008$) and 167 g heavier than the reducers ($p = 0.04$). The adjusted mean infant birth weight of infants born to the reducers was 92 g heavier than that among the no changers ($p = 0.08$). White reducers with baseline cotinine levels greater than 100 ng/mL had infants who were 241 g heavier than did White no changers. A 220-g difference was also seen in Black reducers with a baseline cotinine level of 100 ng/mL or less. Although smoking cessation increased infant gestational age at delivery by 1 week, smoking reduction had little effect. CONCLUSION: Cotinine-validated smoking reduction rates were positively associated with an increase in infant birth weight. While smoking cessation must continue to be the primary objective for pregnant smokers, specific intervention methods should also be directed toward smoking reduction for women who cannot quit.

Measuring Quality of Life in Asthma—EF Juniper, GH Guyatt, PJ Ferrie, LE Griffith. Am Rev Respir Dis 1993;147:832.

The aim of this study was to evaluate the measurement properties of an Asthma Quality of Life Questionnaire. The study design was an 8-wk unblinded single cohort with assessments at 0, 4, and 8 wk. Thirty-nine adults with symptomatic asthma and a wide range of airway responsiveness and medication requirements were enrolled from previous studies and through notices in the local media. Those with inadequately controlled asthma were offered an inhaled steroid (budesonide). Asthma Quality of Life Questionnaire, spirometry, a clinical asthma control questionnaire, medication requirements, airway responsiveness to methacholine, the Sickness Impact Profile, and the Rand questionnaire were recorded at each visit. Patients kept daily diaries of peak flowrates and medications. The Asthma Quality of Life Questionnaire was able to detect changes in patients who responded to treatment or who had natural fluctuations in their asthma ($p < 0.001$) and to differentiate these patients from those who remained stable ($p < 0.001$). The Questionnaire was reproducible in patients who were stable (intraclass correlation coefficient = 0.92). There were significant longitudinal and cross-sectional correlations between asthma quality of life and other measures of both clinical asthma and generic quality of life. We conclude that the Asthma Quality of Life Questionnaire has good measurement properties and that it is valid as both an evaluative and a discriminative instrument. It measures the component of asthma most important to patients, and it should be considered for inclusion in all asthma studies.

Objective Measurement of Patterns of Nasal CPAP Use by Patients with Obstructive Sleep Apnea—NB Kribbs, AI Pack, LR Kline, PL Smith, AR Schwartz, NM Schubert, et al. Am Rev Respir Dis 1993;147:887.

Obstruction of the upper airway during sleep (OSAS) is widely treated by having patients self-administer nasal continuous positive airway pressure (CPAP). To obtain objective evidence of the patterns of CPAP use, information was gathered from two urban sites on 35 OSAS patients who were prescribed CPAP for a total of 3,743 days. Patients were given CPAP machines that contained a microprocessor and monitor that measured actual pressure at the mask for every minute of each 24-h day for an average of 106 days per patient. They were not aware of the monitor inside the CPAP machines. Monitor output was compared with patients' diagnostic status, pretreatment clinical and demographic characteristics, and follow-up self-reports

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of CPAP use, problems, side effects, and aspects of daytime fatigue and sleepiness. Patients attempted to use CPAP an average of 66 ± 37% of the days monitored. When CPAP was used, the mean duration of use was 4.88 ± 1.97 h. However, patients' reports of the duration of CPAP use overestimated actual use by 69 ± 110 min ($p < 0.002$). Both frequency and duration of CPAP use in the first month reliably predicted use in the third month ($p < 0.0001$). Although the majority (60%) of patients claimed to use CPAP nightly, only 16 of 35 (46%) met criteria for regular use, defined by at least 4 h of CPAP administered on 70% of the days monitored. Relative to less regular users, these 16 patients had more years of education ($p = 0.05$), and were more likely to work in professional occupations. At pretreatment they tended to report more episodes of daytime sleepiness ($p = 0.062$) and less ability to perform tasks ($p = 0.069$), and at follow-up after CPAP use they reported greater satisfaction with CPAP ($p = 0.025$) and an improved level of daytime energy ($p = 0.046$). The most frequently cited problems with CPAP were "inconvenience" (54%) and "stuffy nose" (46%), although the complaint that the mask caused "claustrophobia" was the only problem identified significantly more often by the 19 patients who used CPAP less regularly ($p < 0.02$). Surprisingly, only 2 of the 35 patients studied used CPAP for at least 7 h on 70% of days, suggesting that frequent, long-duration, quality sleep is a relatively rare occurrence in OSAS patients treated with CPAP. We conclude that actual CPAP use by OSAS patients falls short of the therapeutic goal of providing quality sleep all night, every night, and that patients' self-reports are rather poor estimates of actual use within and between nights. Efforts to enhance CPAP use are needed, especially early in treatment.

Postoperative Pulmonary Complications: Epidural Analgesia Using Bupivacaine and Opioids versus Parenteral Opioids—C Jayr, H Thomas, A Rey, F Farhat, P Lasser, J-L Bourgain. Anesthesiology 1993; 78:666.

BACKGROUND: Different types of analgesia have been proposed for the prevention of postoperative respiratory complications. The aim of this prospective, double-blind randomized study was to compare the impact of epidural bupivacaine and opioids vs parenteral opioids on respiratory complications in patients who had undergone major abdominal surgery. METHODS: One hundred fifty-three patients undergoing abdominal surgery for cancer were randomly allocated to receive either general anesthesia with intravenous fentanyl and postoperative analgesia with subcutaneous morphine (SC group) or general anesthesia combined with epidural bupivacaine and epidural bupivacaine plus morphine for postoperative pain relief (EP group). Analgesia was tested on a visual analog pain scale. Pulmonary complications were evaluated according to clinical complications, chest radiographs, arterial blood gas analysis, and pulmonary function tests. The evaluation was carried out on the day before the operation and on the first 5 postoperative days. Particular attention also was paid to the episodes of arterial hypotension and hemoglobin oxygen desaturation during the 1st postoperative night. RESULTS: Pain relief was significantly better in the EP group than in the SC group ($p < 0.05$) especially during recovery and on the 1st and 2nd postoperative days. In the EP group, vital capacity decreased less on the 1st postoperative day ($p < 0.05$) and arterial oxygen tension was greater in the recovery room ($p < 0.05$). However, no statistically significant difference was observed between the SC and EP groups in the incidence of clinical pulmonary complications (31% and 27%, respectively) and radiographic chest abnormalities (52% and 46%, respectively). The EP group recovered intestinal function earlier ($p < 0.05$), but significantly more patients in this group had episodes of systolic hypotension (21% vs 8%; $p < 0.05$) during the 1st postoperative night. The length of the hospital stay was similar in both groups of treatment. CONCLUSIONS: Epidural analgesia with a combination of local anesthetic and opioid improves patient comfort. However, this type of analgesia does not decrease the incidence of postoperative pulmonary complications, does not reduce the length of the hospital stay, and carries the risk of complications from episodic systemic hypotension.

The Effect of Cricoid Pressure on Preventing Gastric Insufflation in Infants and Children—RJ Moynihan, JG Brock-Utne, JH Archer, LH Feld, TR Kreitzman. Anesthesiology 1993;78:652.

BACKGROUND: The use of cricoid pressure for the possible prevention of regurgitation of gastric contents during induction of anesthesia in both adults and children has been recommended. However, equally important is the technique in possibly preventing insufflation of gas into the stomach. This study was designed to determine the efficacy of cricoid pressure application in preventing gastric gas insufflation in pediatric patients and to determine the airway pressure at which gas entered the stomach (pop-off point). METHODS: Fifty-nine patients, 2 weeks to 8 yr of age, physical status 1-4, scheduled for elective surgery, received an inhalational induction of anesthesia with halothane, N_2O, and O_2. A single observer used a stethoscope to auscultate over the upper

abdomen for any air entry. In Study I (without paralysis), the proximal airway pressure was slowly increased by gradually closing the pop-off valve on the anesthesia machine until gas was heard entering the stomach (pop-off point) or until the peak inspiratory pressure (PIP) reached 40 cm H_2O. Thereafter, the pressurization procedure was repeated three times, altering the application and removal of cricoid pressure. The same patients were then paralyzed (Study II), and the stomach evacuated before commencing an identical pressurization sequence with and without cricoid pressure. RESULTS: Appropriately applied cricoid pressure was 100% effective in preventing gas insufflation into the stomach of all children up to 40 cm H_2O PIP with and without paralysis. In addition, paralysis significantly decreased the median pop-off point in any given patient. CONCLUSIONS: Appropriate application of cricoid pressure prevents gastric gas insufflation during airway management via mask up to 40 cm H_2O PIP in infants and children. An additional benefit of cricoid pressure occurs in paralyzed patients in whom gastric insufflation occurs at lower inflation pressures.

Maximum Voluntary Ventilation: Spirometric Determinants in Chronic Obstructive Pulmonary Disease Patients and Normal Subjects—TA Dillard, OW Hnatiuk, TR McCumber. Am Rev Respir Dis 1993;147:870.

The 12-s maximum voluntary ventilation (MVV) provides an estimate of the ventilatory reserves available to meet the physiologic demands of exercise. Earlier studies established a general relationship between MVV and FEV_1. We hypothesized that the resting maximum inspiratory flow-rate (MIFR) also serves as a clinically useful predictor of the MVV. A total of 105 subjects, 45 women and 60 men (age 57 ± 5 yr, mean ± SD), with expiratory impairment categories of severe (n = 26), moderate (n = 22), mild (n = 18), and normal (n = 39) based on FEV_1 (percentage of predicted), comprised the study samples. The ratio MVV/FEV_1 averaged 41 ± 7 overall. The FEV_1 correlated with MVV in normal subjects ($p < 0.05$, $r^2 = 0.642$) and patients ($p < 0.05$, $r^2 = 0.787$) better than MIFR ($p < 005$, $r^2 \geq 0.480$). MIFR joined with FEV_1 in multiple linear regression to significantly improve the description of MVV: MVV L/min = 30.77 FEV_1 (L) + 5.94 MIFR (L/s) −4.77 (n = 105; $p < 0.05$, $r^2 = 0.849$). The 95% confidence limits for MVV varied from 90 to 110% of predicted from the equation for this sample. The factors sex and impairment category did not reduce the unexplained variability in MVV after inclusion of FEV_1 and MIFR as covariates in ANOVA ($p > 0.05$). Addition of MIFR to the model with FEV_1 produced greater improvement in r^2 than P_{tmax}. We conclude that MIFR, although secondary in importance to FEV_1, is a significant determinant of MVV in patients with COPD and normal subjects. Estimation of MVV from FEV_1 alone is less accurate than either direct measurement of MVV or estimation by inclusion of MIFR.

The Effectiveness of Pressure Support Ventilation for Mechanical Ventilatory Support in Children—H Tokioka, M Kinjo, M Hirakawa. Anesthesiology 1993;78:880.

BACKGROUND: The rapid respiratory frequency of children may lead to patient-ventilator asynchrony and increase the work of breathing during mechanical ventilation, and the use of a small endotracheal tube and a demand valve can further increase this work of breathing. Athough pressure support ventilation (PSV) is well known to reduce the work of breathing in adults, there are no reports regarding clinical studies of PSV in children. Therefore, the effect of PSV on breathing patterns and the work of breathing in children was studied. METHODS: Six children (3-5 y of age) were studied in the immediate postoperative period. Three levels of PSV, 0, 5, and 10 cm H_2O, were employed. Airway pressure, flow, tidal volume, minute ventilation, and respiratory frequency were measured. To assess the work of breathing, the negative deflection of esophageal pressure (ΔP_{es}) caused by inspiratory effort was measured. The inspiratory work of breathing was also estimated directly by measuring the esophageal pressure-volume loop using the Campbell technique. RESULTS: Although minute ventilation did not change with PSV, tidal volume increased and respiratory frequency decreased with increasing levels of PSV. The ΔP_{es} decreased markedly from 8.9 cm H_2O with PSV of 0 cm H_2O to 5.7 cm H_2O with PSV of 5 cm H_2O and 2.7 cm H_2O with PSV of 10 cm H_2O. The mechanical work of breathing also decreased from 0.743 Joules/L with PSV of 0 cm H_2O to 0.463 Joules/L with PSV of 5 cm H_2O and 0.196 Joules/L with PSV of 10 cm H_2O. CONCLUSIONS: It was concluded that PSV can effectively augment spontaneous breathing and reduce the work of breathing in children.

Effects of One Night without Nasal CPAP Treatment on Sleep and Sleepiness in Patients with Obstructive Sleep Apnea—NB Kribbs, AI Pack, LR Kline, JE Getsy, JS Schuett, JN Henry, et al. Am Rev Respir Dis 1993;147:1162.

Nasal continuous positive airway pressure (CPAP) has become the nonsurgical treatment of choice for obstructive sleep apnea syndrome (OSAS). Recent evidence suggests

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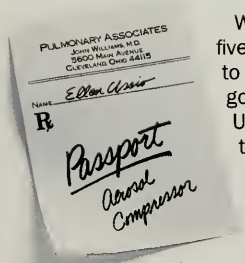
that intermittent use of CPAP by patients is more common than nightly compliance. To determine the consequences of intermittent CPAP use, in terms of a return of sleep-disordered breathing and daytime hypersomnolence, 15 OSAS subjects were evaluated at three times: (1) before CPAP treatment (pretreatment), (2) after 30 to 237 days post-treatment during a night of CPAP use (on CPAP), and (3) during a night without CPAP (off CPAP). Evaluations of sleep-disordered breathing and three domains of hypersomnolence, physiologic sleep tendency, subjective sleepiness, and performance, were accomplished with the respiratory disturbance index (RDI), multiple sleep latency test (MSLT), Stanford sleepiness scale (SSS), and psychomotor vigilance task (PVT), respectively. CPAP use was encouraged and monitored from pretreatment to post-treatment by daily diaries for most subjects and an electronic device for a subset of subjects. As expected, CPAP eliminated apneas and hypopneas, and following the on-CPAP night, there were statistically significant improvements in objective measures of sleepiness (MSLT and PVT). Subjective measures of sleepiness and fatigue also showed improvement. Sleeping without CPAP for one night reversed virtually all of the sleep and daytime alertness gains derived from sleeping with CPAP. This occurred despite a statistically significant reduction in the RDI on the night off CPAP [mean (SD) = 36.8 (28.0) events/h) relative to the pretreatment night [56.6 (24.8) events/h], which may be due to a lessening of the edema of the upper airway following CPAP use. The results of the study suggest that failure to use CPAP for even a single night can result in reappearance of pretreatment levels of nocturnal sleep disturbance and daytime hypersomnolence, even though the rate of respiratory events may be lessened.

Adequacy of Prescribing Positive Airway Pressure Therapy by Mask for Sleep Apnea on the Basis of a Partial-Night Trial—MH Sanders, NB Kern, JP Costantino, RA Stiller, K Studnicki, J Coates, et al. Am Rev Respir Dis 1993;147:1169.

We tested the hypothesis that a prescription for positive-pressure therapy (including pressure level, patient-device interface, and positive-pressure modality, eg, CPAP or BiPAP™) for obstructive sleep apnea (OSA) can be developed on the same night as the polysomnographic (PSG) diagnosis is made. Fifty consecutive patients with OSA in whom a partial-night PSG diagnosis was made (PSG_D) underwent a therapeutic trial of positive-pressure therapy during the remainder of the night ($PSG\text{-}PP_P$). The average apnea index during PSG_D was 54.96 ± 36.3 (mean ± SD). On a subsequent full-night PSG ($PSG\text{-}PP_F$), the prescription was tested. Thirty-one of the 50 patients were satisfactorily treated with CPAP, without variation of the interface during both $PSG\text{-}PP_P$ and $PSG\text{-}PP_F$. In these patients the average pressure prescription while receiving $PSG\text{-}PP_F$ was statistically higher than during $PSG\text{-}PP_P$ (11.77 ± 3.6 vs 10.56 ± 3.6 cm H_2O, respectively, $p = 0.002$). In 14 of these 31 patients (45%) some alteration in pressure requirement was necessary during PSG- PP_F. Eleven patients required 2.5 cm H_2O higher pressure and three patients required 5 cm H_2O higher pressure during $PSG\text{-}PP_F$ than during $PSG\text{-}PP_P$. There was a change of interface across the two therapeutic trials in 15 patients. Although the average pressure required by the 10 of these patients who continued to receive CPAP (ie, did not require a change to BiPAP) was statistically the same across both trials (13 ± 3.5 vs 14 ± 2.9 cm H_2O, $PSG\text{-}PP_P$ and $PSG\text{-}PP_F$, respectively, $p = 0.22$), six of them required 2.5 cm H_2O more pressure, and one required 5 cm H_2O less pressure during the full-night trial. This distribution of pressure changes appeared similar to that observed in patients who maintained the same interface during both PSG tests. Eight patients required a change in positive-pressure modality across the two trials. Of these, seven changed from CPAP to BiPAP during $PSG\text{-}PP_F$. We conclude that although a majority of patients with OSA can obtain a satisfactory prescription for positive-pressure therapy on the same night as the diagnosis is made, a substantial proportion of them will require alterations of that prescription, including changes in pressure, patient-device interface, or positive-pressure modality.

Transtracheal Delivery of Gas Decreases the Oxygen Cost of Breathing—J Benditt, M Pollock, J Roa, B Celli. Am Rev Respir Dis 1993; 147:1207.

Transtracheally administered gases decrease inspired minute ventilation in both dogs and humans. To test if this is associated with a decrease in the oxygen cost of breathing and to evaluate subsequent changes in the breathing pattern, we studied five patients with chronic respiratory diseases while they spontaneously breathed air and different flows of tracheally administered gases. In a blinded crossover design, the gas consisted of either oxygen or air at 2, 4, and 6 L/min. Oxygen cost of breathing was estimated by the calculation of pleural pressure-time index (PPTI). The pattern of breathing was evaluated utilizing the tension time index for the diaphragm (TTdi). There were significant decreases in PPTI when the patients received 2, 4, and 6 L/min of transtracheal oxygen or air. TTdi also decreased as gas flow increased. This drop was significant at 6 L/min flow for both gases. We conclude that transtracheally



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administered gas reduces the oxygen cost of breathing. It also changes the respiratory pattern of the diaphragm to a less demanding pattern. This may offer an alternative form of treatment to rest overworked respiratory muscles.

Evaluation of a New Ambulatory Spirometer for Measuring Forced Expiratory Volume in One Second and Peak Expiratory Flow Rate—DP Johns, M Abramson, G Bowes. Am Rev Respir Dis 1993;147:1245.

A new pocket-sized ambulatory spirometer (meter) that measures FEV_1 and PEFR was evaluated. The meter determines flow rate ($\dot{V}$) from the differential pressure (P1–P2) across a sharp-edged orifice ($\dot{V} \propto \sqrt{[P1-P2]}$). Ten meters were evaluated for accuracy using a computerized syringe to deliver the 24 ATS-recommended waveforms and 9 scaled versions of a single waveform (PW#24). Within-meter reproducibility of FEV_1 and PEFR was evaluated in 2 meters by passing 5 versions of waveform PW#24 through each meter 10 times. Reliability in the ambulatory setting was assessed in 6 meters on several occasions over a 10-wk period using 5 versions of waveform PW#24. Results show that the 10 meters conform to the ATS accuracy specifications for PEFR with 1 or less errors and marginally outside these limits for FEV_1 with 4 errors. For the 9 versions of PW#24, the 95% confidence intervals indicate that the meter is accurate to within ±5.5% or ±15 L/min for PEFR and ±3.5% or ±0.12 L for FEV_1. The mean within-meter coefficient of variation was 1.24% for FEV_1 and 0.35% for PEFR. There was no significant change in meter accuracy or performance over the 10-wk reliability study. We conclude that the meter is suitable for use as an ambulatory spirometer for measuring FEV_1 and PEFR.

Prevalence and Characteristics of Nutritional Depletion in Patients with Stable COPD Eligible for Pulmonary Rehabilitation—AMWJ Schols, PB Soeters, AMC Dingemans, R Mostert, PJ Frantzen, EFM Wouters. Am Rev Respir Dis 1993; 147:1151.

Prevalence and characteristics of nutritional depletion were established by body composition measurements in 255 COPD patients in stable clinical condition admitted to a pulmonary rehabilitation center. Depletion of body weight, fat-free mass (using bioelectrical resistance measurements), and muscle mass [from creatinine height index (CHI) and mid-arm muscle circumference] was most pronounced (40 to 50%) in patients suffering from chronic hypoxemia and in normoxemic patients with severe airflow obstruction (FEV_1 < 35%) but also occurred in ±25% of patients with moderate airflow obstruction. Classification of the patients in four groups by body weight and fat-free mass revealed that depletion of fat-free mass may occur in normal-weight COPD patients (Group 3). These patients also exhibit a decreased CHI (61 ± 21%, mean ± SD) and suffer from physical impairment (12-min walking distance, WD, 532 ± 152 m) to an even greater degree than underweight patients with relative preservation of fat-free mass (Group 2) (CHI = 73 ± 16%; WD = 744 ± 233 m). No systematic differences were established between the four groups in serum protein concentrations or medication use. We conclude that fat-free mass is a better indicator of body mass depletion than body weight. Classification of COPD patients by body weight *and* fat-free mass may have consequences for planning and interpretation of intervention strategies, particularly in Group 2 and 3 patients.

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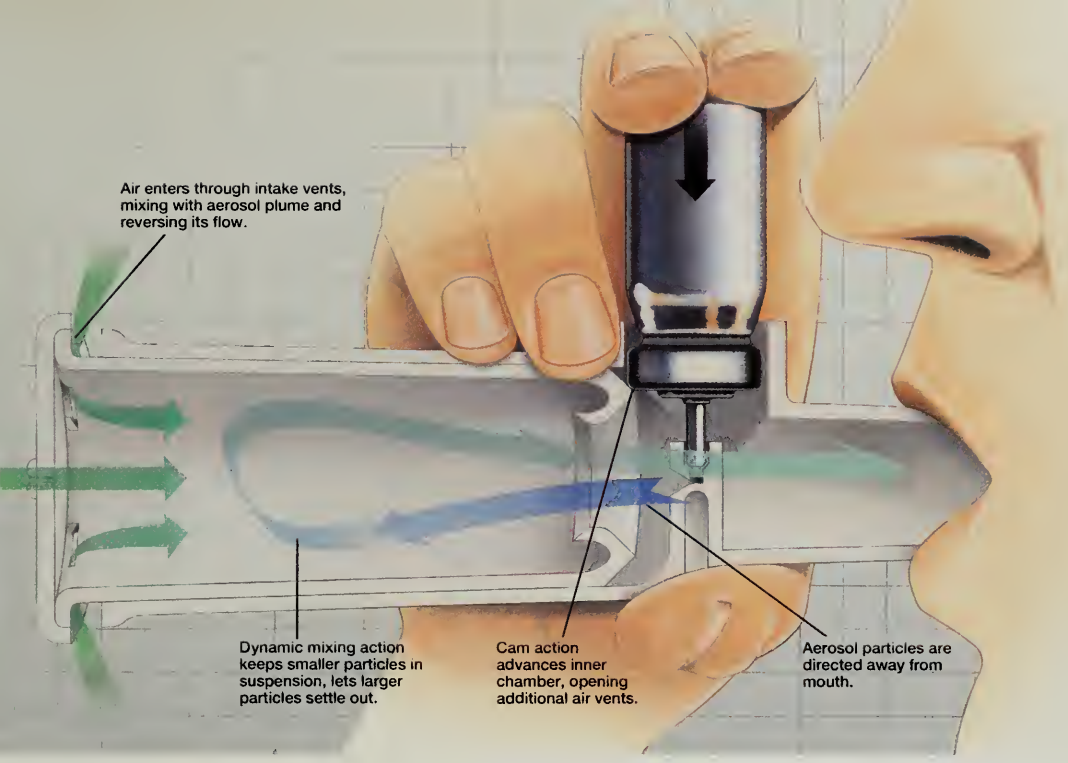
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OXYGENATION IN THE CRITICALLY ILL PATIENT

Part I

A Special Issue

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Dear Reader:

The American Association for Respiratory Care and its science journal RESPIRATORY CARE are proud to present the June and July 1993 issues containing the proceedings from the 1992 Journal Conference—Oxygenation in the Critically Ill Patient. The papers and discussions presented here are well-organized, state-of-the-art materials designed for you to use in your daily practice.

Considerable planning and work are required to present and publish the proceedings of a conference like this. We are grateful to the speakers, the Editorial Board, Conference Co-Chairmen Dean Hess MEd RRT and David J Pierson MD, Editor Pat Brougher, and Editorial Coordinator Donna Stephens for planning, writing, editing, and participating in the Conference and sharing this important information with us.

We are indebted to Allen & Hanburys, Division of Glaxo Inc, for their generous grant to the Association, which made possible the presentation and publication of the Conference proceedings. Allen & Hanburys has supported the last five Journal Conferences, for which we are enormously grateful.

Sincerely,

Ray Masferrer RRT
Managing Editor
RESPIRATORY CARE

Oxygen Toxicity in the Critically Ill Patient

Charles G Durbin Jr MD and KK Wallace MD

I. Background
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III. Clinical Studies: Normal Human Lungs
IV. Clinical Studies: Abnormal Human Lungs
V. Morphologic Patterns of Oxygen Toxicity
VI. Biochemistry of Oxygen Free Radicals
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Background

The assumption that high inspired oxygen concentrations are damaging to the lung is a long-held belief. In 1775, Joseph Priestley, the discoverer of oxygen (O_2), indicated that oxygen might be beneficial in some human disease states but noted

> For as a candle burns out much faster in dephlogisted [oxygen] than common air, so *we* might, as may be said, live out too fast, and the powers be too soon exhausted in this pure kind of air.[1]

One of the guiding clinical maxims in the treatment of respiratory failure is that 100% inspired oxygen [at sea level] for as few as several days induces irreversible lung damage and must be avoided. Reduction in inspired oxygen fraction (F_{IO_2}) to a 'safe level' is a goal in almost all clinical approaches to the treatment of hypoxic respiratory failure. Because the event causing respiratory failure is often transient, distant, and complete by the time hypoxia is identified, "avoid oxygen toxicity" is often the intensivist's main treatment recommendation.

Much is known about oxygen toxicity in healthy human and animal lungs. Many clinical ideas and recommendations about treatment originate from studies of animal models, tissue culture, and chemical models. The toxic effects of high F_{IO_2} in injured human lungs have not been studied. For ethical and technical reasons, these needed proofs cannot be obtained, and the belief that oxygen is toxic to injured lungs will continue to be based on indirect evidence and extrapolation of nonhuman experiments. But, as has been said, "Absence of proof [of effect] is not proof of absence [of effect]." Despite this lack of direct evidence of toxic effects in the injured lung, the overwhelming majority of experimental data support the position that high F_{IO_2} is deleterious even to damaged lungs.

The goal of this paper is to review the available data on oxygen toxicity in critically ill human patients. However, the lack of useful information on this condition makes firm conclusions impossible. Our bias is that high F_{IO_2} does indeed contribute in some patients to a poorer outcome and that attention to reduction in F_{IO_2} is an appropriate therapeutic goal. We shed little light on the magnitude of the additional injury that is caused by high F_{IO_2} and do not defend a particular F_{IO_2} as being toxic

Dr Durbin is Professor of Anesthesiology and Surgery, and Dr Wallace is Professor of Radiology—University of Virginia Health Sciences Center, Charlottesville, Virginia.

A version of this paper was presented by Dr Durbin on October 9, 1992, during the RESPIRATORY CARE Journal Conference on Oxygenation in the Critically Ill Patient, held in Puerto Vallarta, Mexico.

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or safe. The main argument we propose supporting the contribution of high F_{IO_2} in increasing lung injury is that (at least) early in the development of hypoxic respiratory failure, the pathologic distribution of the injury is inhomogeneous. Usually, the adult respiratory distress syndrome (ARDS) is thought of as a uniform process involving the entire lung, and the plain chest radiograph demonstrates homogeneous increased density throughout all lung fields. In fact, if the appearance is nonhomogeneous, the diagnosis of ARDS is often questioned. However, on more sensitive radiographic examination and in tissue samples, normal-appearing lung units are found to be interspersed with abnormal lung units. This is particularly true early in the course of the disease. It is probable, then, that high F_{IO_2} produces O_2 toxic lesions in the 'normal' areas, with the same characteristics and same time course as seen with oxygen toxicity in normal human lungs and animal models.

We begin with a brief review of the pathology and symptomatology of oxygen toxicity in normal human beings and then review oxygen-induced biochemical events and cellular responses. The inhomogeneous nature of lung disease and the nature of O_2 tolerance in animals are then described. Finally, we integrate these ideas into a rational model and suggest clinical correlations in the ICU population. Treatment strategies based on the model are suggested and areas for future investigations identified.

Normobaric Oxygen Toxicity in Normal Human Lungs: Introduction

For this paper, only those studies employing normobaric oxygen (≤ 1 atmosphere of pressure) are cited. The effects and uses of hyperbaric O_2 have recently been reviewed[2] and are not within the scope of this paper. All organs demonstrate damage when exposed to high levels of O_2; however, the lung is most severely affected in intact animals because P_{O_2} is higher in lung tissue than in any other organ in the body during O_2 inhalation. It should be apparent that the important variable determining toxic potential is the partial pressure of O_2 in the inspired mixture, rather than the F_{IO_2} per se.[3] However, F_{IO_2} is commonly reported in the literature. Care must be exercised in evaluating clinical reports in patients treated at higher altitudes because F_{IO_2} underestimates tissue P_{O_2} under these conditions. For example, at 6,000 feet (approximate altitude of Denver, Colorado), 100% O_2 results in an alveolar P_{O_2} of only 552 torr rather than the 713 torr at sea level.

Other organs besides the lung are affected by increased P_{O_2}. Acute organism toxicity is usually manifested by neurologic alterations. These begin with excitation and culminate with seizures. These manifestations are generally seen only with O_2 above 1 atmosphere of pressure.[2,4,5]

Clinical Studies: Normal Human Lungs

Breathing 100% O_2 for more than several hours causes demonstrable changes in normal volunteers. Symptoms, including cough and substernal tightness, occur after a variable period. Bronchoscopy reveals tracheitis, with mucosal hyperemia and edema. There is also decreased bronchociliary movement of secretions at the time these symptoms appear.[6] No abnormalities in pulmonary function tests have been demonstrated in volunteers with < 12 hours of 100% O_2 breathing. A decrease in vital capacity (VC) is the first change consistently demonstrated in volunteers during prolonged O_2 breathing. This occurs after 24-30 hours at F_{IO_2} of 1.0 and after longer periods at lower F_{IO_2}.

Time-concentration or oxygen-dose values correlate with VC reduction and have been used by the U.S. military as indices of the potential severity of O_2 toxicity. Because of individual variation in VC-maneuver performance and the effects of prior exposure to O_2, the value and reliability of this index have been called into question.[7] Caldwell et al[8] have shown a decrease in carbon monoxide diffusion capacity and static compliance after 48 hours of 100% O_2 breathing. Their study of normal volunteers also demonstrated changes in lung compliance. Atelectasis was suggested as the cause for the increased alveolar-arterial gradient for O_2 [$P_{(A-a)O_2}$]. However, the changes observed were not readily reversible in one subject, suggesting structural injury. Brain-dead patients demonstrated pulmonary deterioration when maintained on 100% O_2.[9] The major finding was an increased $P_{(A-a)O_2}$. Pathologic examination of the lungs was of little help in delineating the cause because both controls and study

patients had complicating lung pathology and received positive-pressure ventilation as well. It is clear that pathologic pulmonary changes can occur in normal lungs exposed to 100% O_2 > 24 hours. The occurrence of lung injury after shorter duration and with < 100% O_2 has also been seen.

Analysis of lung fluid after 17 hours of 100% O_2 breathing in humans demonstrated increased capillary permeability (alveolar-capillary leak), with albumin and transferrin appearing during bronchial alveolar lavage (BAL).[10] Longer exposures at lower F_{IO_2}s also caused these changes. Griffith et al[11] demonstrated albumin leakage at F_{IO_2} 0.30-0.50 after 48 hours. If protein leak is a marker of oxygen toxicity, then the potential for damage of normal lungs exists even at low F_{IO_2}.

Clinical Studies: Abnormal Human Lungs

Evidence demonstrating either safety or harm from high F_{IO_2} in human diseased lung is minimal. Singer et al[12] showed no objective changes in patients maintained on an F_{IO_2} of 1.0 versus < 0.42 for an average of > 21 hours after open heart surgery. A letter to the editor in *Lancet* indicated that there was no evidence of oxygen toxicity after up to 42 days of high frequency ventilation on 100% O_2.[13] The authors suggested that high peak airway pressure and airway pressure changes may be more important than high F_{IO_2} in causing lung damage. There are anecdotal reports of individuals surviving weeks to months on 100% O_2. It is apparent from animal studies that the presence of pre-existing lung disease may afford some protection from the development of lethal O_2 toxicity.[14] Large clinical studies are needed to estimate the magnitude of this protective effect in humans and to define the conditions under which it occurs. A first step would be the development of a large clinical data set to identify the patterns of O_2 use and survival in the critically ill. A lung injury score is needed to establish severity of illness and give some clues to the answers to these questions.

Morphologic Patterns of Oxygen Toxicity

Few pathologic studies have been reported in humans early in the course of ARDS. Marked changes in lung morphology are seen at autopsy in patients dying after prolonged illness.[9] The effects of all these modes of respiratory support, other illnesses, and progression of disease are reflected in this material. The changes seen cannot be directly equated with oxygen administration. Most important studies of the pathology of oxygen toxicity involve animal species. Marked differences exist between species in the tolerance to and manifestations of oxygen toxicity.[15-17] One must be cautious when applying these animal findings to human disease. The sequence of changes is similar in most other species and man, but the duration and dose of oxygen exposure needed to produce pathologic changes vary widely. The specific cellular changes are different between primates and other mammals, which further confuses the pathologic interpretation.

The initiating event in O_2 toxicity is chemical. There is an increase in production of partially reduced oxygen molecules, with no change in cellular morphology. Figure 1 is an electron micrograph of a normal human alveolar septum.[18] The thin alveolar epithelial cell (dark arrow) is in close approximation to the capillary endothelium, which is also very thin. The thick cell side is the capillary side of the gas exchange unit (*).

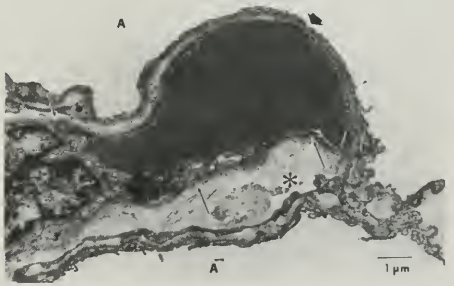

Fig. 1. Electron micrograph of a normal human lung. The thin alveolar cell is identified by the black arrow, which is is separated from the capillary by a thin basement membrane. The * indicates the thick side of the capillary, the metabolically active area. The small arrows indicate the tight junctions between the capillary endothelial cells. (Reprinted from Reference 18, with permission.)

Following the increase in production of partially reduced O_2 molecules, free radicals form. These molecules damage cellular elements and lead to an increase in endothelial cell thickness and accumula-

tion of perivascular fluid. Figure 2 shows a human alveolar septum early in the course of ARDS.[18] There is increased fluid in the space between the alveolar epithelium and capillary endothelium (*). Gross cell structure is maintained, but simplification of intercellular components has occurred, and the cell thickness is increased. Gas exchange may be altered in this setting. These findings are widespread but not uniform throughout the lung at this stage.

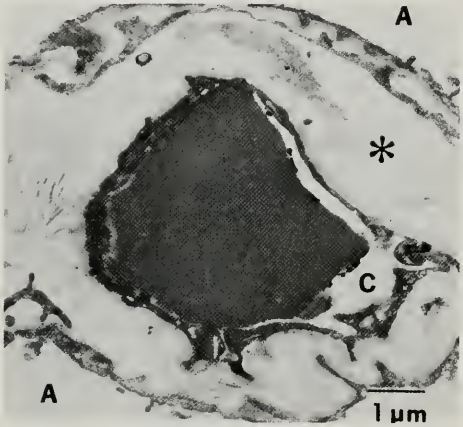

Fig. 2. Electron micrograph of an alveolar septum in an early stage of edema from ARDS. The space between the epithelium and endothelium is markedly expanded, as shown by the *. Some alveolar swelling has occurred. (Reprinted from Reference 18, with permission.)

A rapid infiltration of inflammatory cells, including macrophages and neutrophils, follows this early phase. Figure 3 demonstrates a neutrophil migrating through the capillary junction into the interstitium.[19] These cells release inflammatory mediators that augment the local destructive response. Inflammatory mediators can be detected in airway fluid at this time.

With increased extravascular fluid, bronchiolar edema leads to patchy alveolar collapse and hyaline membrane formation. This alters distribution of ventilation, producing the deterioration in gas exchange seen with oxygen toxicity and other forms of ARDS.[20,21] Neutrophils are believed to contribute to the destruction of lung architecture because they increase production of O_2 radicals and

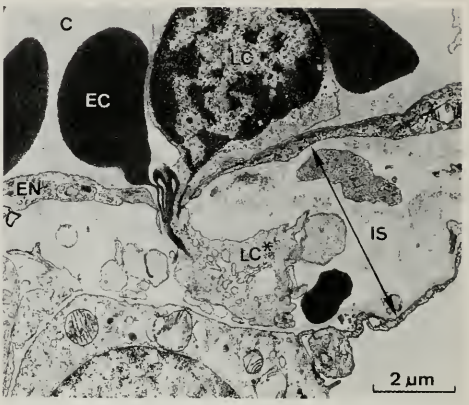

Fig. 3. As ARDS progresses, neutrophils infiltrate the interstitium. In this electron micrograph, a leukocyte (LC) is passing from a pulmonary capillary into the interstitium. Some endothelial swelling has occurred. The epithelial cells are normal. (Reprinted from Reference 19, with permission.)

other inflammatory mediators in the presence of high F_{IO_2}.[22] These mediators migrate through the endothelial cell junctions shortly after the beginning of O_2 toxicity. Endothelial cell junctions become less tight and allow more fluid and cellular material, including red cells, to pass into the interstitium. Neutropenic animals, although somewhat O_2 resistant, still manifest these pathologic responses to increased F_{IO_2};[23,24] thus, neutrophils are not essential to the production of toxic-oxygen lesions. Neutrophils are not essential for the development of ARDS in humans, either.[25] The final lesion in O_2 toxicity in nonprimates is endothelial cell destruction. There is only minimal alveolar cell change in these species.[26]

In humans and other primates, O_2 toxicity causes proportionately more alveolar (epithelial) cell morphologic change. Figure 4 is an electron micrograph from a man dying 7 hours after the onset of lethal hemorrhagic shock.[19] There is focal destruction of the alveolar epithelial cells, with preservation of the endothelium. In the lethal phase, Type-1 cells (thin, alveolar lining cells) are progressively replaced by Type-2 (columnar epithelial) cells. In monkeys, the alveolar Type-1 cells are completely replaced with these columnar cell within 7 days of 100% O_2 exposure.[27] A similar

morphologic change is seen in humans. Type-2 cells are immature forms and can differentiate into Type-1 cells during resolution of lung injury. They are metabolically active and probably responsible for O_2 tolerance in advanced injury. With continuing exposure to O_2, infiltration of fibroblasts and deposition of collagen are seen. These cells are oxygen tolerant and proliferate in continued hyperoxic lungs. Obliteration of the pulmonary vasculature results from lung remodeling. This probably accounts for the persistent, irreversible pulmonary hypertension seen in primates after recovery from severe O_2 toxicity.[28]

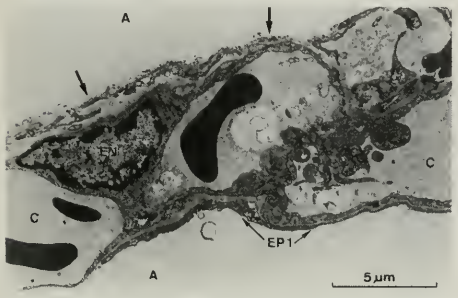

Fig. 4. In animals, the final injury of O_2 toxicity is alveolar epithelial cell destruction, as seen in this electron micrograph. The arrows indicate areas of damage in this patient, 7 hours after the onset of hemorrhagic shock. The other side of this septum shows well-preserved alveolar cells. (Reprinted from Reference 19, with permission.)

ARDS presents a pathologic picture identical to that described for O_2 toxicity. In fact, hyperoxia is used by some investigators as a model for studying ARDS. This is one of the most important confounding issues in investigating the safety of O_2 in humans with hypoxic lung disease. When the toxic side effects of the treatment are similar to the manifestation of the primary disease, any attempt to separate the contributions of each is doomed to failure.

Biochemistry of Oxygen Free Radicals

The presumed basis of the toxic effect of high F_{IO_2} on the lung is magnified formation of O_2 free radicals. These highly reactive species are capable of oxidizing many cellular components. Because they are normal by-products of cellular oxidation, most cells have developed elaborate protective systems to detoxify them. With normal O_2 exposure, these mechanisms are adequate to protect the cell from massive damage. In hyperoxic conditions, large quantities of these intermediaries are produced, overwhelming the protective systems.[29] Due to the extremely high O_2 concentrations in lung tissue during O_2 breathing, the lung is particularly at risk for damage from O_2 free radicals.

Table 1. Toxic Products of Oxygen Reduction

Species	Structure	Toxicity
Superoxide anion	O_2^-	Normal product
Hydrogen peroxide	H_2O_2	Easily handled
Hydroxyl free radical	OH	Very toxic
Singlet O_2	$^1O_2$	Very toxic

The hydroxyl free radical ($OH^{\cdot}$) and oxygen singlet ($^1O_2$) are the most important in producing pulmonary injury.[30] Other free radicals are illustrated in Table 1. Normal cellular enzymatic processes produce and detoxify most of the free radicals. These normal processes are illustrated in Figure 5. In conditions of excess, superoxide dismutase converts the oxide anion to hydrogen peroxide, a less toxic compound that is further degraded by catalase. Sulfhydryl groups, such as those in glutathione, are avid scavengers and are reduced as cofactors by catalase. Other soluble protective agents are tocopherol, ascorbate, and beta-carotene. These protect cell membranes and other cellular elements from oxidant injury. These protective mechanisms are illustrated in Figure 6.

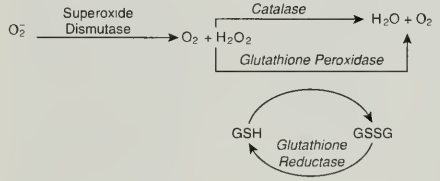

Fig. 5. Schematic diagram of the normal detoxification of oxygen singlets ($^1O_2$). Normal enzymatic pathways produce less toxic hydrogen peroxide and protect the cell from damage. Hydrogen peroxide is degraded by catalase. GSH = reduced glutathione; GSSG = oxidized glutathione.

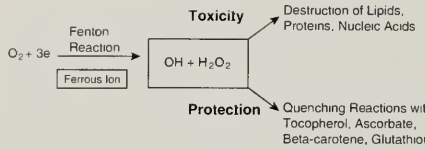

Fig. 6. The Fenton Reaction produces the most toxic hydroxyl ion in the presence of ferrous ion. This free radical reacts with lipids, proteins, and nucleic acids. Protective mechanisms include glutathione and quenching reactions with tocopherol, ascorbate, and ß-carotene.

The effects of reactive products are widespread. Intracellular proteins and nucleic acids can be altered and inactivated. Possibly the most important effects are mediated by attack on lipids. This leads to activation of phospholipase and production of arachadonic acid metabolites. These include the leukotrienes and prostaglandins, which have profound local vascular effects. They may increase edema, attract neutrophils and macrophages, and dilate or constrict blood vessels and bronchi. Further progression of O_2-induced lung injury may be through this mechanism. The effect on surfactant production in O_2-induced injury is unknown. Different models demonstrate normal or only slightly decreased surfactant production until the last stage of injury, when surfactant is markedly diminished.[31] Surfactant administration ameliorates O_2 toxic injury in some models.[32,33]

Production of O_2 free radicals is an important initial event in the development of oxygen toxicity. Factors that seem to increase oxygen tolerance or resistance involve the systems for protection from tissue damage due to these moieties and are discussed later.

Heterogeneity in Acute Hypoxic Lung Injury

In many forms of hypoxic lung injury, it is apparent that the injury is not homogeneous. For instance, hypoxia due to aspiration pneumonia is produced by perfusion of the affected lung areas, usually the dependent, posterior segments. The remainder of the lung segments are normal. Increased inspired O_2 is preferentially distributed to the 'good' areas of lung—those areas that have the best compliance. These normal areas of lung have the highest exposure to O_2 and the highest potential for damage. The potential contribution of high F_{IO_2} to worsening outcome in ARDS rests on the assumption that the initial injury results in a heterogeneous pattern of disease. This implies that relatively normal areas are distributed among abnormal areas. Injured areas of ARDS lung are probably relatively protected from further injury because the local tissue P_{O_2} is likely to be low due to limited diffusion through edema and collapsed tissues. The assumption of inhomogeneity is borne out by several observations.

As patients become ill they increase their minute ventilation markedly but maintain relatively good oxygen exchange (although requiring increased F_{IO_2}). Their tachypnea is probably due to decreased pulmonary compliance from increased interstitial fluid. Initially, lung architecture is relatively normal.[20] As perivascular edema increases, bronchiolar obstruction occurs, and some alveoli collapse while others remain normally ventilated and perfused. Hypoxia ensues as blood flow to these collapsed alveoli continues.

PEEP, or positive end-expiratory pressure, opens up some of these collapsed alveoli (alveolar recruitment), and better matching of ventilation and perfusion occurs. If these alveoli were not anatomically normal (or at least more normal than other involved alveoli), then PEEP would have no effect on oxygenation except to shunt blood away from normal lung units. This would worsen oxygenation. In some disease states, PEEP does decrease oxygenation due to this mechanism. PEEP, in isolated lung disease such as single-lung surgery or lobar pneumonia, often adversely affects oxygenation by redirecting blood to disease-involved areas.[34] Thus, because PEEP improves oxygenation in ARDS, there must be a large number of 'normal' collapsed alveolar units. This is particularly true early in the course of the development of ARDS.

Lungs of patients or animals with ARDS and O_2 toxicity demonstrate areas of normal lung architecture and areas of total collapse early in the disease course. Figure 7 is a low-powered conventional micrograph of lung obtained 3 days after the onset of ARDS related to uncontrolled septicemia in a young woman.[19] Edema fluid in the alveolus is apparent, the architecture is well preserved, and

normal and abnormal alveoli are present. The progression of O_2 toxicity is illustrated in Figures 8-10 from sheep exposed to 100% O_2 for 7 days.[35] Initially, little diffuse change is seen, and normal areas predominate. As exposure continues, the changes become more widespread, but there are spared, normal-appearing areas. Even in the final, premorbid state, some lung units are spared.

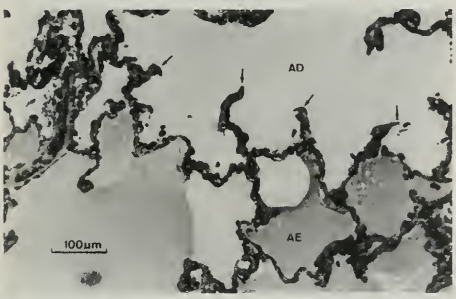

Fig. 7. Light micrograph of lung tissue from a young woman who died on the third day following the onset of septicemia. The inhomogeneity of the lesion is apparent. (Reprinted from Reference 19, with permission.)

Radiographic evidence supports these pathologic impressions. The gross distribution of pathology can be studied at various stages of the disease. On computed tomographic (CT) examinations, inhomogeneous disease is usually seen.[36,37] Figure 11 is a chest radiograph from a 34-year-old woman, 3 days after the onset of symptoms consistent with early ARDS. Diffuse fluffy infiltrates are uniformly distributed throughout all lung fields. A CT scan obtained the same day to evaluate intra-abdominal pathology shows marked variation in lung consoli-

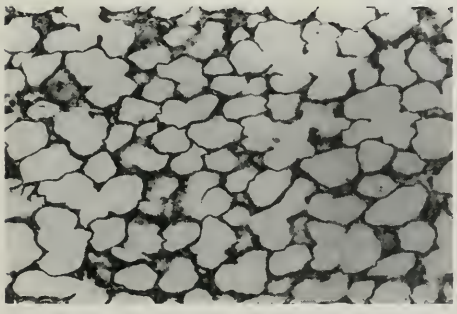

Fig. 8. Light micrograph of normal sheep lung. (Reprinted from Reference 35:2333, with permission.)

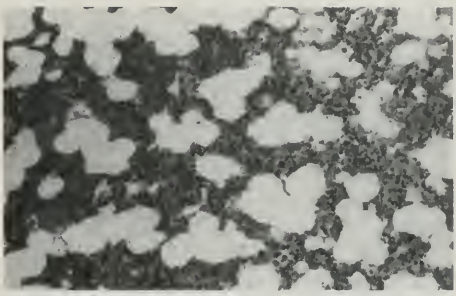

Fig. 9. Light micrograph of sheep lung after 68 hours of O_2 breathing. Alveolar walls are thickened in most areas; however, some normal alveoli are present. (Reprinted from Reference 35:2333, with permission.)

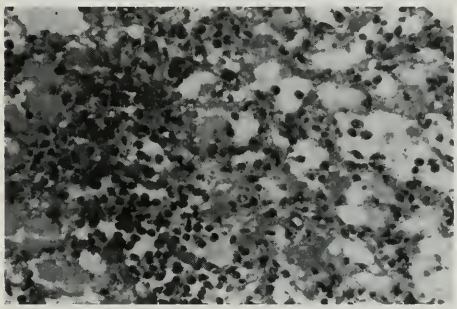

Fig. 10. Light micrograph of sheep lung after 84 hours of O_2 breathing. Diffuse edema, cellular infiltrates, and alveolar fluid are seen. Several normal-appearing areas are present in this micrograph. (Reprinted from Reference 35:2333, with permission.)

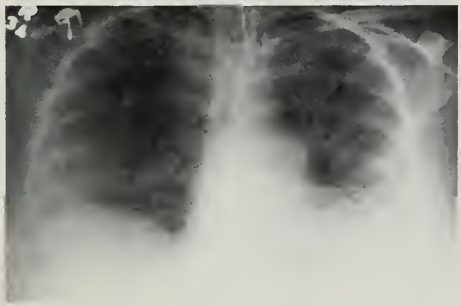

Fig. 11. Portable chest radiograph of a 34-year-old woman, 3 days after the onset of respiratory distress. Diffuse panlobar infiltrates are seen.

Fig. 12. Three representative cuts from an abdominal CT scan obtained the same day as the radiograph in Figure 11. The dark areas represent normal pulmonary anatomy. The white areas are disease-involved. The patchy nature of ARDS is apparent in these radiographs.

dation mixed with areas of normal-appearing lung. Normal lung appears as dark areas in the CT scan shown in Figure 12 A-C.

The chest radiograph of another patient, a 47-year-old woman 7 days after the onset of ARDS, is shown in Figure 13. In addition to the diffuse, generalized increased density in all lung fields, there is a marked increase in density in the right midlung zone. Surprisingly, a CT scan in this patient shows a completely normal right-lower-lobe segment overlying a consolidated middle lobe (Figs. 14 A & B). These two cases and others in the literature confirm the inhomogeneous nature of ARDS. The toxic potential of O_2 in generalized lung injury is likely to be manifested by damage to the remaining normal areas. Collapsed areas are not likely to be exposed to high tissue levels of O_2, and injury itself may increase protective processes.

Fig. 13. Chest radiograph of a 47-year-old woman, 7 days after the onset of ARDS. Patchy infiltrates with a predominance in the midlung fields are seen.

Alteration of Oxygen Sensitivity

Susceptibility to O_2 injury varies widely among animal species. Most species demonstrate oxygen tolerance induction by various methods. Age is also an important determinant of susceptibility.[15] Young animals are more resistant than older animals to the deleterious effects of high F_{IO_2}. This may be due to their ability to increase levels of protective en-

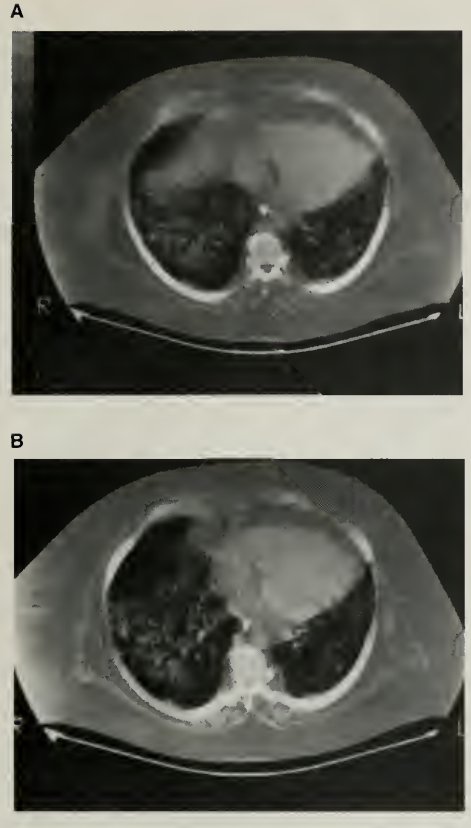

Fig. 14. CT scan of patient in Figure 13. In addition to the inhomogeneous distribution of disease in the posterior areas, complete sparing of an anterior segment is seen.

zymes. A marker of this protective response may be the inducibility of the activity of the cytochrome p-450 system.[16] Animals with enhanced ability to increase p-450 metabolic activity suffer less from high F_{IO_2}. However, generalized increased metabolism (such as occurs with hyperthermia or hyperthyroidism) increases susceptibility to O_2 injury.[4] This is due to increased rate of toxic radical formation and more rapid tissue turnover.

Endogenous steroid administration magnifies toxicity, whereas adrenalectomy, surgical or medical, improves survival in animals exposed to 100% O_2. Steroids given at the peak of toxicity may improve survival, due to enhanced protective enzyme activity or, more likely, to the reduction of fibroblast proliferation. Epinephrine and other catecholamines magnify the O_2 injury.[4,38-40]

Dietary factors are very important in altering animal survival under hyperoxia. Protein malnutrition increases O_2 toxicity. Sulfur-containing amino acids are particularly important in maintaining antioxidant cellular function. Vitamin C, E, and A deficiencies magnify the toxic effects of O_2. Absence of trace metals, especially selenium and copper, also magnifies the O_2 toxic lesion. Iron is a cofactor for free radical production in the Fenton Reaction, and high serum or local levels may magnify the toxic effects of O_2. This effect has been demonstrated in tissue culture systems but not in whole animals. This may be of concern in hemorrhagic lung injuries, where tissue levels of iron may augment the production of O_2 radicals.[4]

Certain chemotherapeutic agents augment O_2-induced lung injury. Bleomycin causes a progressive pulmonary fibrotic injury that is augmented even by low F_{IO_2}. This effect is long-lasting; and even months after completion of treatment, O_2 exposure can cause rapid progression of the lung injury.[41,42] This has major implications for respiratory care practitioners because patients exposed to this drug in the past may much later develop irreversible respiratory failure on routine O_2 administration. Adriamycin produces a similar toxic effect, although the heart seems to be the most sensitive target organ, and delayed injury is less common. Other cancer treatment agents may have similar effects, and lung toxicity is often the limiting factor in their use.[41,42]

One of the most intriguing findings is that previous exposure to sublethal concentrations or duration of O_2 increases O_2 tolerance. Almost all species studied demonstrate this phenomenon.[26,43] This may be due to anatomic changes in cell structure or an increase in protective enzymes. In light of the clinical approach to O_2 therapy in humans, this may be one reason that O_2 toxicity is difficult to identify with certainty.

Endotoxin exposure also induces O_2 tolerance in rats and other animals,[44] due to induction of antioxidant systems.[45] Endotoxin is often a cause of ARDS in humans and may contribute to O_2 tolerance.

Clinical Implications

The development of oxygen toxicity is a concern in normal lungs. It probably contributes to some extent to injury in diseased lungs as well. The magnitude of the contribution to poor outcome depends on the degree of heterogeneity of lung units. Normal units are most likely more susceptible to O_2 damage than abnormal units. Even in diseases thought of as being homogeneous, such as ARDS, patches of normal lung can be found early in the course of disease. The attention clinicians pay to high oxygen levels is justified.

Oxygen toxicity occurs at O_2 levels less than 100%. In animal models and cell cultures, toxic effects can be demonstrated in low ranges: F_{IO_2} 0.30-0.50. A model for describing the toxic potential for oxygen is shown in Figure 15. Oxygen-resistant and susceptible animals behave differently. As F_{IO_2} approaches 1.0, the harm in all cases increases. Oxygen resistance diminishes the lethality of even high F_{IO_2}s. Oxygen tolerance in animal and cell culture models can be induced by prior sublethal O_2 exposure, appropriate diet, vitamin supplements, and endotoxin. Because endotoxin and prior sublethal O_2 exposure are common in critical illness, our speculation is that they may confer some protection on patients.

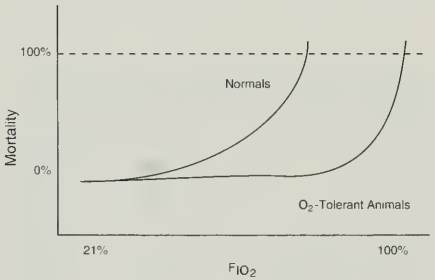

Fig. 15. The relationship between oxygen exposure (F_{IO_2}) and mortality is illustrated. Oxygen-tolerant animals survive longer than normal animals.

If humans respond as animals do, the technique of administering O_2 may alter the development of O_2 toxicity. Periodic 'bursts' of 100% O_2 may increase survival in otherwise lethal conditions. Gradual increase in F_{IO_2} may improve outcome as well. High F_{IO_2} during the middle or at the end of an illness may not be as significant as at the onset. This is supported clinically, as long survival on F_{IO_2} 1.0 is occasionally seen. Within 7 days of the onset of ARDS, the alveolar Type 1 cells are uniformly absent from the lung, having been replaced with Type 2, columnar cells. These cells are relatively O_2 resistant and can replace the missing Type 2 cells during pulmonary recovery. The value of administration of antioxidants and free radical scavengers awaits confirmation in human disease. The effects of airway pressure on development of lung injury and augmentation of O_2 toxicity have not been evaluated. Current attention to limiting the F_{IO_2} by accepting lower P_{aO_2}, decreasing mechanical ventilation (accepting higher P_{aCO_2}), and using artificial gas exchange techniques (IVOX and ECMO) are exciting areas of research. The exact role of O_2 administration in worsening outcome in the already injured lung will probably never be known for certain.

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Durbin Discussion

Morris: The pathologic changes may be rather late changes (analogous to the crackles we hear in early lung edema, a very late change in the sequence of events that precedes the development of alveolar flooding). So, there may already be marked changes in enzymatic complements in the cells and the ability of the cell to protect itself from oxygen. There may be changes in peroxisomes; there may be changes in superoxide dismutase, glutathione peroxidase catalase, etc. It is commonly argued that 100% oxygen is toxic but lower levels may be safe. While there may be protection against oxygen toxicity by tumor necrosis factor (TNF) and other bioactive substances, it also seems conceivable to me to mount the argument that 21% oxygen might also in some patients be maximally toxic. As far as I know, biologists believe that the development of our antioxidant cellular mechanisms has been an important component of evolution (enabling us to survive in this oxidative environment), which was not present in early years when life was emerging (even before Dantzker was born). So, I've often wondered in the ICU whether there might not be a population of cells that cannot protect itself from ambient oxygen.

Given all of those things, given the fact that screening of trauma patients—Frank Cerra, maybe you can help me with this—has indicated that from the very first blood specimen obtained, TNF has been documented to be present in both the patients who develop ARDS and the patients who don't develop ARDS even though at risk, it looks like there are a lot of mediators floating around very early. If TNF is involved in the endotoxin effect on oxygen toxicity, who knows what in Heaven's name this means. One's reminded of the (I think it was Myron Laver and his colleagues in the 50s at the MGH) report of a patient who had been supported for about a month with 100% oxygen and survived. That report was interesting because, I think, the general belief was that it was not possible. In addition, we're human and we're not rats. Bottom line—how in Heaven's name are we going to do an animal experiment that's going to provide any information to help Dave Pierson make a decision next year in a patient who's sick, supported with a ventilator, and on high oxygen! I contend the only way we can get the kind of data that will help us in clinical decision making will be to do the appropriate clinical trials with the appropriate definitions. They will be difficult to do, but I think they will be informative.

Hudson: But how would you design that study? What would you use?

Dantzker: That's Morris's hypoxic treatment for hypoxemia!

Durbin: There are two things that may help. One is a large ICU database. There are anecdotal reports, like Myron Laver's that you mentioned. There's a report in the Lancet of 42 patients who were treated with 100% oxygen for a month,[1] with "high frequency" ventilation, and that's what saved them—because of the airway changes. That's a Letter to the Editor; it's not a scientifically valid study.[1] But with large databases, such as are collected with the APACHE or other systems, if one of the variables reported is oxygen dose (and we're not used to thinking of that as a variable), we may get some large population studies that allow us to piece together some of this information.

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Morris: We will come back to that at some point—what to do with these large databases (which, in fact, constitute the major focus of governmental intervention) and whether they will produce useful information.

Hudson: Alan, I can't imagine doing that study. We know how hard all of these studies are to do, but to design this study especially for what we really want to know, which is not do we use 80 to 100% oxygen versus 30%. What we really want to know are the differences in a much smaller range than that. I can't imagine how we could justify keeping patients who might not need it on a high concentration of oxygen. I just don't know how you'd do that.

Morris: Would you consider the difference between 100% and 80% to be an important difference? Or 80% and 60%? I'm asking. When you're designing a study the first question is, What would you perceive to be a difference that would lead to some credible conclusions—a difference that would lead to actions? So, what difference would be useful?

Hudson: We're arguing a lot about the difference between 40% and 70%.

Morris: Between 40% and 70%.

Hudson: Between 40% and 60% or 70%. The problem I'm having right now is that some of my colleagues are using fairly high levels of PEEP in some patients in order to get them to an F_{IO_2} of 0.3. To me that makes no sense because I can't think of any evidence that suggests that an F_{IO_2} of 0.4 or even 0.5 is significantly toxic in the way that we're talking about.

Morris: Right, right. And, one of the problems is co-factors, right? And anybody who's breathing 35% oxygen is probably not sick enough to die from a pulmonary problem. So, that there may be other things happening—I mean they could die of primary pulmonary hypertension and other causes, but in terms of acute hypoxic injury. Let me just suggest one way that one might pursue it is to write two protocols, one that drives patients to 100% oxygen and a low PEEP, and another that drives patients to 70% oxygen and a higher PEEP for sick patients. But, you could make a number of combinations. Now, there are two variables, but at least one could address the issue of whether high pressure and low oxygen produces a different outcome from low pressure and high oxygen. That would advance us significantly. We could talk about other schemes, but I don't think we can do it independently because the number of variables is so large and because we're human. We can't manage that, as human physicians. I think we might be able to do it with decision support.

Wood: I use less F_{IO_2}—with all the uncertainties that exist and with no data to back it up except the following notion gleaned from the 150 studies that you used to make your conclusions. It seems to me that if oxygen radicals are a mediator of the acute lung injury in animals and in humans, and if oxygen radicals are at least part of the mediator of the acute lung injury of ARDS or its variants, then there is a prior rationale for delivering fewer oxygen radicals in the inspired gas. I put my bias out on the table, and you can find others with an opposite bias—like, use more F_{IO_2}. Given opposite biases, it gets easier to do the study that Len (Hudson) and Alan (Morris) are talking about. So, I'd like to be in the 40% group. Anybody around the table who wants to can be in the 70% group. Now, we have a legitimate question, Does 40% inspired O_2 reduce mortality and morbidity compared to 70% F_{IO_2}? Yet, the study design must accommodate other differences between the 2 groups because the 40% group may require some other interventions (more PEEP, more cardiac output) to ensure adequate oxygen delivery. That's the basis for the study, and I agree that it is a 'do-able' study and also agree with Alan Morris's comment that an answer to this question never falls out of a broad database. You must prospectively ask the question, control as much else as possible, and compare the end points for statistical differences. And then you have a faint chance of being able to get that question answered. We have answered a lot of equally obscure questions, and this one probably matters.

Dantzker: Well, I think it's also not going to come out of animal studies. We have watched animal studies for 15 years, and I don't think there's any more understanding—just a lot of money spent. We learned a lot about antioxidants in rats, but we learned very little else. Rats are very sensitive animals. It's interesting that if researchers had looked at oxygen toxicity in another animal first, they might not have gotten very excited. Mice are much more resistant than rats, and I remember visiting Buzz Johanson at the Southwest Research Institute and seeing his baboons—in these big chambers and kept at 80% oxygen. The baboons all died of sepsis because the cages couldn't be cleaned out well enough. The baboons really did have a lot of oxygen toxicity after 6 or 7 days when they started to get septic and sick from the environment—and that's probably as close to humans as you can get. So, I think animal studies are not going to help. I think the problem with the study that you guys are talking about is that the number of confounding variables is going to be immense. I mean, if you want to keep somebody alive, you're either going to have to give them high inflation pressures or you're going to have to give them high oxygen. We already know from recent animal models what high inflation pressures do.[1] And you have to wonder whether a lot of the damage that you see—I think back to that one article in the *New England Journal*, that wonderful study where they took brain-dead people and ventilated them on high oxygen for a few days and then autopsied them.[2] They found all these changes, but, of course, they were probably using big inflation pressures. We know they used 15 mL/kg or whatever in those days. Who knows whether any of the changes they saw had anything to do with oxygen or whether it really had to do with high inflation pressures. I think it's going to be a difficult question. I guess I intuitively go along with what Larry (Wood) said, which is probably less is better, although I don't have any evidence for that.

1. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137: 1159-1164.
2. Barber RE, Hamilton WK. Oxygen toxicity in man: a prospective study in patients with irreversible brain damage. N Engl J Med 1970;283(27): 1478-1484.

Durbin: One of the things that I hoped would come out of yesterday's talk was that maybe we don't need as high a P_{O_2} in the blood as we have thought, and that would solve a couple of issues.

Dantzker: Well, that may be true.

Durbin: But we didn't come up with a number like 40 or 20 torr, and say that was OK. Or maybe we have a different monitor, and, therefore, some of this becomes moot. I'm also concerned about the papers that come out of places like Utah that are at high altitude. We have to remember that it's not really F_{IO_2} that counts. It's ambient partial pressure of oxygen that matters. If you're at sea level, then 100% is not the same as it is in Denver.

Cerra: The implication has been that inspired oxygen per se is an oxygen radical producer. I think the evidence for that is pretty scant. The evidence is that oxygen radicals are endogenously produced by a number of cells in response to some effector agent. You have to make that distinction clear.

Durbin: In regard to wound healing, —alveolar partial pressure is very high, even with 21% inspired O_2 and tissue P_{O_2} is greater than 40 torr in the lung. I'm not sure that this model applies to the lung per se. Also, wound healing involves the phase of collagen deposition, and I'm not sure I want collagen deposition in a healing lung. That may destroy architecture and end up with fibrosis. The lung may be a unique organ in this regard.

Huang: I guess I should say something about this topic. We've been involved in oxygen toxicity studies at Duke over the last 5 years using a primate model. I think a primate model is a good viable alternative to determine the threshold for oxygenation in humans, considering the difficulties that we have all faced in clinical trials. The response to oxygen in primates is certainly different from the responses that we see in the lower animals. I think those studies done in lower animals cannot be applied directly to humans. One good example is oxygen tolerance. While oxygen tolerance has been shown in rodents, the same results have not been shown in any other models, including primates. Second, I want to make a general comment on oxidant injuries. In the last 10 or 20 years of trials, antioxidants did not consistently help prevent oxidant injury in all models, including sepsis and hyperoxia. Of course, one of the problems is that the antioxidant isn't readily getting into the cell, especially in the ischemic areas. Oxidant injury is really an imbalance between the oxidant production and the antioxidant defense mechanism in our body. The antioxygen defense mechanism may be different in different individuals. This may determine the individual susceptibility to oxidant injury and may account for the variability of oxygen toxicity. I agree that there may be no safe oxygen level because oxidant injury can occur even at room air. A good example is ischemia-reperfusion lung injury, which could occur in ARDS in some areas where there is ischemia due to occlusion by thrombus in microcirculations. When these patients get better, these areas reopen, and may result in a local ischemia-reperfusion injury. We should really try to keep the inspired oxygen concentration as low as possible; 40% or even 35% is probably OK in many patients, but may not be so in others.

Wood: I want to turn the topic for a moment to the so-called proliferative phase of the acute lung injury to get a related question on the table. It seems to me that there is a change in the clinical course of some patients when they begin to develop higher static pressure on the ventilator, increased dead-space-to-tidal-volume ratio (V_D/V_T) signalled by increased minute ventilation, pulmonary hypertension, and a few radiologic changes suggesting pulmonary interstitial fibrosis with dilated bronchioles—these features characterize that population as sliding into the proliferative phase. They seem to have a much worse prognosis. The questions I haven't addressed are, What precipitates that second phase? Is high F_{IO_2} implicated? And what is the incidence of patients with acute lung injury who go into the phase of disordered healing?

Nelson: Charlie (Durbin), I'd like to ask you two other thing about high oxygen fractions. I think John Downs has suggested that in patients he's looked at,[1] the problem of absorption atelectasis in the ICU is real. It does occur at oxygen fractions probably below 50%, and certainly everything above 50%, and is one possible harm of acute oxygen exposure. Also, what about the problem of paralysis in mucociliary transport that supposedly occurs at oxygen fractions over about 40%? I'd just like to hear your thoughts and the group's thoughts about those two potential harms, even though they're not classic oxygen toxicity.

1. Register SD, Downs JB. Is 50% oxygen harmful? Crit Care Med 1984; 12:327.

Durbin: Absorption atelectasis certainly can be demonstrated, whether it has long-term consequences, and whether it's prevented by low F_{IO_2} is not clear. Certainly you're correct in

concerns about ciliary motility and mucosecretion removal, which are diminished by intubation, with or without high inspired oxygen. But I'm not sure if it's any different at 100% than at 30%, or even 21% F_{IO_2}. Others might want to comment on this.

Dantzker: About absorption atelectasis—we looked for years, when we were doing inert gas studies, in which every patient we studied always got a short course of 100% oxygen. We saw, I think, occasional older, normal subjects who developed a little bit of shunt following 100% oxygen breathing. But, interestingly enough, in our patients with obstructive lung disease, for example, we never saw an increase in shunt after breathing 100% oxygen. I think in those cases there's so much collateral ventilation that it's probably not a problem. I think it's hard to say whether you'd see it in ARDS because all those patients are always breathing high oxygen to begin with and have big shunts. They have too many other things that affect the level of shunt. I think that in interstitial disease you also don't see it with 100% oxygen. So, I think that absorption atelectasis is really much less of a clinical problem than has been thought.

Pierson: Before you move on, may I poll this group as to our current practice? Let's say that you have a young patient with ARDS, fully resuscitated. You've done all the good things: You have the patient on 10 cm H_2O of PEEP and 60% oxygen. P_{O_2} is in the 60s. How many would hold there, rather than manipulating PEEP, etc, in order to further lower the F_{IO_2}? We have 5 hands.

Morris: That's only one of the options. If you formulate your questions correctly, you come up with . . .

Pierson: It may be impossible to poll this group on anything!

Dantzker: But you have to let Alan (Morris) frame the question.

Morris: In science, in general, much of what we obtain in terms of knowledge base is defined by the questions we ask. So, it's not a trivial issue. It's not my idea. I take no credit for this observation.

Pierson: But it's also maybe not like at the bedside.

Morris: Exactly. If you ask only questions about how the heart is working, you won't ever pick up a seminoma.

Pierson: Let's assume that the scenario I have posed is after you've done all the other things you choose to do, including working up the seminoma. So, this patient on 60%, 10 of PEEP, P_{O_2} in the 60s, and everything else that you elected to do . . .

Dantzker: The 60s. You said 60 before.

Pierson: The 60s. P_{O_2} in the 60s. Now, I'm not going to hold anybody to this, but I'm trying to move us toward the *real* fight that's coming later this afternoon. How many would manipulate *something*? Make some change to get the O_2 down to at least 50%? That's 12 hands. Let's say that you did that, and you were able to get the patient down to 50%. How many would do further maneuvers to try to get it below that, down into the 40s?

Morris: What's the P_{O_2}?

Pierson: P_{O_2} is now around 58. How many would do further things, up the PEEP, lower the O_2, to get the O_2 down to 40%? Larry (Wood) and Loren (Nelson). OK. This is maybe a silly exercise, but . . .

Morris: I was just remembering the last antioxidant study results that came across my desk. You'll remember the study. It's a randomized trial of acetylcysteine inhalation that produced no evidence of benefit. I don't know, maybe it wasn't done correctly—what's the right dose, maybe, there are lots of maybes—but, in fact, the bottom line is when people have looked to see if antioxidant therapy in one form or another would produce a beneficial effect, they've found none. Now, I once again ask myself whether it is important to focus upon the ciliary beat frequency? Is it important to focus upon mucus blanket? Is it important to focus upon toxic oxygen-intermediate generation? Or is it important to focus on survival? I argue once again that the imperative in medical research and medical care drives us to focus upon survival, upon the relief of pain and suffering. Whether toxic oxygen intermediates go up or down during the genesis of a survival is of great interest and importance for our understanding of biological mechanisms, but I would argue that medicine as a field has become distracted in the last 40 years from its major purpose, and has become attracted to mechanisms rather than the ultimate outcome.

Hudson: This really leads into my topic. I think we've been driven too much by survival, and not looked at other end points. I think we may start to use some of these things that have important biological effects—effects that we can agree might be clinically important—and start to combine them and then have an effect on improving survival, when we can't do a large enough study to show a survival effect with a given agent or a given mechanism.

Morris: Dr Hudson has articulated very well what many people would call a reductionist approach. No, I don't mean it pejoratively. We will be able, if we understand the elements of the system, to predict the output of the intact system. I think that's going to constitute the basis of what may be a small debate today. One that should attract our attention. I think both the reductionist and holistic approaches have defensible arguments.

Pharmacologic Approaches to Respiratory Failure

Leonard D Hudson MD

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Introduction

In the 25 years since the adult respiratory distress syndrome (ARDS) was originally described,[1] the management of patients with this form of hypoxemic respiratory failure has improved. However, no startling breakthroughs have either revolutionized the management or markedly lowered the mortality rate of these patients. Many clinical investigators studying ARDS and related conditions believe that we are now on the verge of such a revolution, not because of the development of any one treatment or agent but because a multitude of pharmacologic agents holding great promise are now on the horizon.[2-4] I am aware of 14 different categories of drugs that have potential benefit in management of ARDS that are either currently in clinical trials or for which clinical trials are being prepared. And because more than one agent frequently exists in a given category of drug, the list of potentially useful agents is indeed impressive. It is not just the number of possible clinical agents that is impressive, but the nature of many of these drugs. They include agents that have greater promise for ameliorating the underlying pathophysiologic process than vir-

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tually any that have previously been considered (other than corticosteroids—a sobering thought).

There are many reasons for this profusion of pharmacologic agents. A primary reason is the vastly improved knowledge regarding the underlying pathophysiology, largely the result of basic research studies on inflammation, as well as more directed research dealing with inflammatory injury in the lungs and other organs. A second reason is the burgeoning biotechnology industry, whose growth has been driven by the rapid entrance of molecular biology into the clinical arena. In other cases, new agents have resulted from a long and steady attack on pathophysiologic abnormalities, such as surfactant dysfunction, which have been known to exist since ARDS was first described. In still other cases, clinically useful agents have resulted from curiosity about naturally occurring substances, such as nitric oxide, with careful observations made regarding their possible therapeutic applications. At present the therapeutic effectiveness still remains largely a potential, and no single agent may result in a striking drop in mortality. However, I am convinced that many of the agents currently under study ultimately will prove to be beneficial in the management of critically ill patients and particularly those with ARDS; it is likely that appropriate application of some combination of these agents will be able to lower mortality.

In this review I cover a variety of agents currently available for use, or currently under active clinical investigation, or nearing a clinical trial. Although not all of the agents directly improve oxygenation, all have the potential of improving oxygenation of the blood and oxygen delivery to the tissues or of preventing worsening oxygenation through their blocking of mechanisms causing organ injury. Currently, virtually all the management of patients with ARDS or multiple organ dysfunction, other than that aimed at the treatment of infection, is supportive in nature. Although some of the new agents also are supportive, we are now entering an era of definitive therapy, that is, treatment aimed at the underlying etiology of organ dysfunction. The combination of new supportive treatments and a variety of agents providing more definitive alterations of the underlying pathophysiology holds great promise for patients with ARDS and multiple organ dysfunction syndrome (MODS)—and also for patients at high risk for these conditions.

This review is divided into discussions of broad groups of pharmacologic agents representing two different strategies for improving outcome in the patient with ARDS and MODS: (1) agents that correct disordered lung physiology and thus improve lung functioning, including oxygenation, and (2) agents directed against lung inflammation (or systemic inflammation, which can affect multiple organs), given either as treatment or prevention. The review is limited to studies performed in humans. Unfortunately, few definitive controlled trials have been brought to completion. Those that have are described, along with any studies that I know to be in progress or under consideration. Other than human studies, only reviews are cited, rather than extensive citation of basic studies or animal model studies supporting the rationale for a particular agent.

Correction of Physiologic Derangements

The severe hypoxemia present in patients with acute lung injury is due to intrapulmonary shunting related to inflammatory pulmonary edema and atelectasis. The pulmonary edema is a result of endothelial and epithelial injury, with increased permeability and leakage of protein-rich edema fluid into the interstitial and alveolar spaces. Surfactant is rendered inactive by the protein-rich fluid, and surfactant production is also likely to be impaired by injury to the alveolar cells producing this substance. The resulting surfactant dysfunction leads to regional atelectasis. The microatelectasis related to surfactant dysfunction is an important physiologic derangement that helps explain the markedly different clinical presentation and course between pulmonary edema related to acute lung injury, on the one hand, and, on the other hand, cardiogenic pulmonary edema, in which surfactant function is largely preserved. Hypoxic pulmonary vasoconstriction (HPV) is a major compensatory mechanism that helps preserve arterial oxygenation. HPV reduces blood flow to the more injured areas of lung, which have the most impaired ventilation—resulting in better matching of perfusion and ventilation throughout the lung. If HPV is impaired, the oxygenation abnormality will be much

more severe. Significant pulmonary hypertension frequently develops in the course of the ARDS and in some cases is severe.[5] Pulmonary hypertension may result in part from pulmonary vasoconstriction. Microthrombosis has also been demonstrated in patients with ARDS, contributing to pulmonary hypertension. Obviously, agents aimed at enhancing HPV may result in worsening pulmonary hypertension, and agents that decrease pulmonary vascular resistance may release HPV and worsen arterial hypoxemia. Therefore, effects on pulmonary blood pressure and arterial oxygen tension should be evaluated when one is studying either class of agents. Several potential mediators of HPV have been identified, and possible interactions exist between mediators of HPV and those involved in acute lung injury.[6]

Virtually all of the pharmacologic agents under consideration to correct physiologic derangements are encompassed in some way in this brief description of the pathophysiology. Two categories of agents are discussed: (1) agents that improve ventilation/perfusion matching or pulmonary hypertension, and (2) agents used to replace surfactant.

Agents that Affect Pulmonary Vascular Tone and/or Ventilation-Perfusion Matching

Almitrine

Almitrine has been shown to increase arterial oxygen tension and decrease arterial CO_2 in patients with chronic obstructive pulmonary disease (COPD). Although almitrine has been demonstrated to increase ventilation due to stimulation of peripheral chemoreceptors in animal models, studies in patients with COPD have shown that almitrine improves pulmonary gas exchange by reducing ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching without an increase in minute ventilation. Three studies of almitrine have been performed in patients with ARDS.[7-9] Short-term infusion of almitrine in patients with ARDS resulted in significant improvement in P_{aO_2} during the administration of the drug.[7,8] The effect was transient, with oxygen tension returning toward baseline within 30 minutes of the stopping of the infusion.[7] Almitrine infusion was associated with a mild increase in the pulmonary artery pressure without changes in cardiac output. Use of the multiple inert gas elimination technique demonstrated that almitrine redistributed pulmonary blood flow from shunt areas to lung units with normal $\dot{V}/\dot{Q}$ ratios. The effect of a single 30-minute infusion of almitrine on pulmonary gas exchange and hemodynamics was compared to the effect of 10 cm H_2O PEEP in patients with ARDS.[8] Almitrine and PEEP resulted in similar improvements in P_{aO_2}. Almitrine was not associated with significant changes in either pulmonary or systemic hemodynamics, whereas PEEP resulted in a statistically significant reduction in mean systemic pressure. A report in abstract form describes a 48-hour administration of almitrine to patients with ARDS, with resultant improvement in pulmonary gas exchange and no significant adverse effect on right ventricular function.[9]

Nitric Oxide

Nitric oxide given as an inhaled gas is a potent pulmonary vasodilator. Because it binds rapidly to hemoglobin and is inactivated, it has no effect on the systemic circulation. Because it is given by inhalation, its vasodilator effect should be limited to the ventilated regions of the lung. Thus, inhaled nitric oxide should selectively improve the perfusion of ventilated regions and reduce intrapulmonary shunting, in contrast to intravenously administered pulmonary vasodilators. Inhalation of nitric oxide was studied in 10 patients with severe ARDS.[10] Seven of the patients were treated with continuous inhalation for periods from 3 to 53 days. A relatively low dose of nitric oxide (18 ppm) resulted in a significant reduction in mean pulmonary artery pressure (from 37 to 30 mm Hg) and also decreased intrapulmonary shunting (from 36 to 31%). The P_{aO_2}/F_{IO_2} also increased significantly during nitric oxide administration. Mean arterial pressure and cardiac output were unchanged. Tachyphylaxis did not occur. This preliminary and uncontrolled study was not designed to test the effect of nitric oxide inhalation on survival.

Surfactant Replacement

Surfactant administration in premature neonates with infant respiratory distress syndrome has re-

sulted in improved oxygenation and improved survival.[11] Surfactant has been known to be abnormal in ARDS since the first report by Ashbaugh and colleagues.[1] Subsequent work has confirmed both quantitative and qualitative abnormalities in surfactant from patients with ARDS,[12,13] and the possibility of surfactant replacement in ARDS patients has been discussed.[14-16] Trials of both artificial surfactant and surfactant derived from animal sources are currently being conducted in adults with ARDS. The dose and route of administration of these viscous substances pose practical problems in adults. Also, theoretic concerns about surfactant replacement in adults exist, because surfactant dysfunction is a secondary rather than primary abnormality in ARDS, and the presence of protein-rich pulmonary edema fluid might inactivate any surfactant administered. Preliminary results of placebo-controlled trials of an aerosolized artificial surfactant found trends toward physiologic improvement and reduced mortality.[17,18] Complete results of these and other ongoing trials are not yet available. In addition to its physiologic properties, surfactant has been shown to inhibit cytokine production (including TNF, IL-1, and IL-6) in LPS-stimulated alveolar macrophages obtained from normal volunteers.[19]

Suppression of Systemic or Alveolar Inflammation

Most of the recent research activity in critically ill patients at risk for or with ARDS or MODS has been directed at the inflammatory process, which is thought to result in and/or perpetuate organ injury.[2] Inflammation normally is a beneficial process that controls and repairs infection or injury. However, in certain circumstances associated with critical illness or injury, it appears that "rogue inflammation"—systemic inflammation that has escaped its usual control mechanisms and has gone berserk—may actually result in organ injury rather than limit it. The process of normal inflammation is complicated—involving an orchestrated wave of chemical signals, cytokines, inflammatory cells and cell products, as well as inhibitors of many of these components. Our knowledge of this normal inflammatory process and of some of the abnormalities present in rogue inflammation has been tremendously advanced by basic research in recent years. This basic information about the biology of inflammation, together with advances in molecular biologic techniques and biotechnology, has resulted in a plethora of agents designed to inhibit or interrupt malignant intravascular inflammation. However, rogue or malignant inflammation does not exist in isolation. Many of the same inflammatory elements have beneficial as well as injurious roles at the same time. Thus, agents aimed at inhibiting or blocking inflammation must be carefully considered, and appropriate studies must be carried out to examine potential adverse effects, particularly on infectious complications and wound or injury repair.

Figure 1 shows a simplified schema by which rogue inflammations result in injury to the lung. Some of the potential elements involved in this malignant inflammatory process are included. The exact triggering events are not listed and in some cases may not be known. Also, the exact sequence of events in the clinical situation may be incorrect. The sequence of events, which elements are involved, and interactions between and among various elements may vary greatly from patient to patient, depending on the clinical circumstances and host-related variables. The neutrophil is shown as playing a prominent role in this schema. Although some clinical and animal model data suggest that lung injury can occur without major involvement

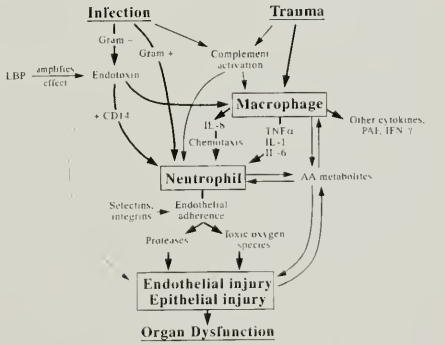

Fig. 1. A simplified schema by which rogue inflammations cause injury to the lung. LBP = lipopolysaccharide-binding protein; IL-1 = interleukin-1; IL-6 = interleukin-6; IL-8 = interleukin-8; TNFa = tumor necrosis factor-alpha; PAF = platelet activating factor; AA = arachidonic acid; and IFNg = interferon-gamma.

of neutrophils,[20,21] a general consensus among investigators supports the neutrophil hypothesis—that is, that neutrophils play a central role in inflammatory lung and other organ injury in most clinical circumstances. The macrophage, both in the blood and the lung, appears to be an important player in this scenario as well. Macrophages and monocytes are sources of cytokines and chemoattractants early in the process and thus are important in the initiation and early propagation of injury. However, we have developed data from serial lung lavages that suggest a beneficial role for alveolar macrophages later in the course of the evolution of inflammation, with an increase in alveolar macrophages correlating with a favorable outcome.[22]

For the purpose of this review I have arbitrarily divided anti-inflammatory agents into two categories: general and specific. Under the category of general anti-inflammatory agents I have included those agents that have the potential for several mechanisms. Even though specific agents may be found to have more than one mechanism, they are intended to block or inhibit a single element of the inflammatory cascade.

General Anti-Inflammatory Agents

Corticosteroids

Intravenous high-dose methylprednisolone sodium succinate is the anti-inflammatory agent that has been most widely and thoroughly studied in humans.[3] A previous study[23] suggested a beneficial effect in patients with septic shock, but the study design was flawed. Subsequently, controlled trials of methylprednisolone have been conducted in surgical patients with major trauma or abdominal surgery at high risk for ARDS,[24] patients with sepsis syndrome or septic shock,[25-28] and patients with already existing ARDS.[29,30] Methylprednisolone was usually administered in high doses for one day, although in one study design it was given for three days.[24] None of these studies showed evidence of benefit with end points including development of ARDS and overall mortality. When corticosteroids were limited to administration for one day, generally there was no evidence of adverse effect in the form of increased infections. However, when methylprednisolone was given to surgical patients for three days, a statistically significant increase in clinical infections occurred in the subsequent week.[24] Thus, abundant evidence indicates that corticosteroids have no significant role in either prevention of ARDS in patients at high risk due to trauma or sepsis or in early treatment of ARDS. One study[31] has demonstrated that corticosteroids given to patients with multiple fractures resulted in a reduced incidence of fat embolism syndrome identified by a scoring system. However, this fat embolism syndrome was not necessarily one that included severe lung injury equating to the clinical definition of ARDS. The fat embolism scoring system used parameters that identified a very mild syndrome that in some cases was subclinical. Essentially no mortality was associated with either the treatment or the placebo group. Thus, it seems unlikely that corticosteroids are warranted for all patients with long-bone fractures in order to prevent a mild clinical syndrome without associated mortality.

A question remains as to whether corticosteroids given in a later stage of ARDS might be associated with benefit.[32] Although there are no randomized controlled studies, three groups have reported series of anecdotal reports describing administering methylprednisolone for several days to patients with established ARDS who either had severe but stable pulmonary function abnormalities or, in fact, were deteriorating after one to two weeks of the syndrome.[33-36] These groups have attempted to rule out pulmonary infection, in one case by open-lung biopsy with culture.[33] All three groups have reported clinical impressions of clinical improvement and survival that were greater than expected for this group of severely ill patients. A controlled trial of corticosteroids given in this circumstance appears to be warranted.

Prostaglandin E_1

A single-center study of prostaglandin E_1 (PGE_1) administration to surgical (primarily trauma) patients with ARDS reported a reduction in mortality.[37] Subsequently, a randomized double-blind multicenter clinical trial with PGE_1 was performed in patients with ARDS following trauma, major surgery, or sepsis.[38] No difference in survival was found in the treatment versus placebo group, and

the investigators concluded that PGE_1 did not enhance survival in patients with established ARDS. PGE_1 does have potent hemodynamic effects in these patients, reducing systemic and pulmonary vascular resistance, with a reduction in blood pressures and increased stroke volume, cardiac output, and heart rate. This was demonstrated both in this multicenter study[38,39] and in three previous studies involving patients with ARDS.[40-42] In these studies demonstrating hemodynamic improvement, there was no evidence of impaired oxygenation. Thus, although PGE_1 is not warranted in all patients with ARDS, a trial of PGE_1 may be indicated in specific patients with severe pulmonary hypertension and associated impairment of cardiac function.

Pentoxyphylline

Pentoxyphylline has several anti-inflammatory and other biologic effects that theoretically may be helpful in preventing organ injury.[2] There are animal data to suggest this, but no human clinical trial has been reported.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs have been widely studied in animal models, with beneficial results.[3] Ibuprofen is the agent that has been most extensively studied. A pilot study of ibuprofen administered as a rectal solution showed trends suggesting a decreased incidence of development of ARDS, a higher rate of reversal of ARDS in patients who did develop the syndrome, and improved survival.[43] These trends were not statistically significant in this small study but provided impetus for a large, multicenter randomized controlled trial of an intravenous form of ibuprofen in patients with sepsis syndrome. This study is approximately two thirds complete at the time of this writing, and no results are yet available regarding efficacy. It is known by safety monitoring that to date there appears to be no adverse effect on renal function, including in patients with mild renal insufficiency at the time of drug administration. In another small controlled trial, ibuprofen administered as a rectal solution to patients with clinical sepsis had an antipyretic effect, but no significant changes were seen in respiratory and hemodynamic parameters.[44]

Specific Anti-Inflammatory Agents

Specific anti-inflammatory agents have been developed against many different mediators of inflammation.[2-4] Also, several different strategies have been used to counteract any given mediator, resulting in more than one type of agent for some mediators. The types of agents developed have included polyclonal and monoclonal antibodies against the mediator, receptor antagonists for a specific mediator, and soluble receptors that bind with the potentially harmful mediator in the blood and render it inactive, with subsequent removal from the circulation.

Antioxidants

Two studies of antioxidant treatment with N-acetylcysteine have been performed in patients with ARDS.[45,46] One small controlled pilot study involving 30 patients[45,47] showed favorable trends in respiratory physiologic variables but found unexpected significant hemodynamic effects with improvement in oxygen delivery, primarily related to an improvement in cardiac output. This trial raises the point that one must be prepared to make observations on important physiologic effects other than those that might have been expected from animal models. A larger randomized double-blind placebo-controlled study from Denmark[46] included 32 patients treated with N-acetylcysteine and 34 patients treated with placebo. No improvement in oxygenation was seen. A trend toward improved total chest compliance was seen in the treatment group, but this was not statistically significant. There was no difference in survival. These investigators did demonstrate that N-acetylcysteine has an anticoagulant effect and speculated that perhaps pulmonary fibrin uptake was diminished during ARDS. Currently, a multicenter trial is being conducted in North America involving N-acetylcysteine and L-2-oxothiazolidine-4-carboxylate.

Inhibitors of Arachidonic Acid Metabolites

Agents have been developed to inhibit arachidonic acid metabolites and specifically 5-lipoxygenases.[2] I am not aware of a clinical trial of these agents to date, although a clinical trial in patients with ARDS is under consideration.

Anticytokines

Cytokines are small proteins that possess a variety of biologic activities that have been associated with significant clinical effects.[4] Two cytokines in particular, tumor necrosis factor (TNF) and interleukin-1 (IL-1), appear to play a major role in causing the systemic effects associated with sepsis syndrome and associated with tissue inflammation and tissue injury. Interleukin-8 (IL-8) is a potent chemoattractant that attracts cellular elements involved in inflammation as well as inducing platelet-activating factor (PAF) and other active substances. These cytokines are considered to be "pro-inflammatory" cytokines, whereas other cytokines, including some of the other interleukins (IL-4 and IL-10) and transforming growth factor-β, are considered to be anti-inflammatory cytokines.

A double-blind controlled trial of IL-1 receptor antagonist (IL-1Ra) has been completed.[4]* A total of 893 patients with systemic inflammatory response syndrome (SIRS) were studied. The overall mortality in patients receiving placebo was 34%, and in patients receiving high-dose IL-1Ra it was 29%, a statistically nonsignificant difference ($p = 0.22$). Evidently a retrospective subset analysis suggested that patients with increasing severity of illness might have greater survival benefit from IL-1Ra. However, such speculations based on subset analyses need to be confirmed in prospective studies designed to critically test the hypothesis. Studies are now being performed utilizing an anti-TNF monoclonal antibody and a TNF-soluble receptor. In addition, clinical trials of anti-inflammatory cytokines, including IL-4 and IL-10, are being performed.

Antiendotoxins

Endotoxin, or lipopolysaccharide, has a potent role in inducing rogue inflammation in patients with gram-negative sepsis. Several strategies to counteract or inhibit endotoxin have been proposed, including antibodies directed against endotoxin and nontoxic endotoxin analogs, which compete with endotoxin for receptor sites. Antibodies against endotoxin have been studied in clinical trials. Several years ago, use of a polyclonal antibody directed against a mutant strain of *E coli,* which resulted in significant antiendotoxin effect, was studied both as a treatment trial in septic shock[48] and as a prevention trial in surgical patients at high risk for septic shock.[49] This polyclonal antibody was demonstrated to reduce mortality in septic shock and to prevent septic shock and reduce mortality in high-risk surgical patients. However, the polyclonal antibody was not suitable for commercial production and carried theoretic risks involving antigenicity. Subsequently, two monoclonal antibodies directed against endotoxin have been developed and studied.[50,51] The study results have been controversial, with confounding variables affecting interpretation,[52,53] and neither agent has been approved for nonexperimental human use. The monoclonal antibody entitled HA-1A showed an improvement in mortality in patients with sepsis syndrome secondary to gram-negative bacteremia, especially those patients with evidence of septic shock.[50] Clinically one cannot differentiate patients whose sepsis syndrome is due to gram-negative bacteria from those with gram-positive sepsis. This introduces a problem in studies aimed at counteracting gram-negative sepsis, such as those employing antiendotoxins, because a much greater number of subjects are necessarily enrolled and treated than will be found to have the desired study condition—gram-negative sepsis—once culture results are available. Thus, a large percentage of the population entered will have no chance of benefiting from the therapy. This was a problem in the HA-1A study.[50] Although the patients with sepsis syndrome who were subsequently found to have gram-negative bacteremia showed a mortality benefit, no difference in mortality was present in the overall study population compared to placebo—suggesting an adverse effect in patients with sepsis syndrome not due to gram-negative bacteria. Also, this particular study suffered from the observation that there was a marked difference among the participating study centers in the efficacy of the anti-

*Fisher CJ Jr, Dhalnaut J-F, Pribble JP, Knaus WA, and the IL-1 Receptor Antagonist Study Group. A study evaluating the safety and efficacy of human recombinant interleukin-1 receptor antagonist in the treatment of patients with sepsis syndrome. Presented at the 13th International Symposium on Intensive Care and Emergency Medicine, March 23, 1993, in Brussels, Belgium.

body in the patients with gram-negative bacteremia. Study of another monoclonal antibody against endotoxin, called E5, showed similar results, although the study failed to show a greater beneficial effect in patients with septic shock than in those with milder forms of sepsis.[52] Studies are currently under way to further examine monoclonal antibodies against endotoxin.

Inhibition of Leukocyte Adhesion Molecules

Leukocyte adherence to the endothelium is a critical step in neutrophil-mediated tissue injury. A microenvironment is created at the interface where the neutrophil is adherent to the endothelium, and toxic oxygen radicals and proteases are produced by the activated neutrophil and delivered into this isolated area. Antiproteases and antioxidants may be present in abundance in the blood but not have access to this microenvironment, allowing uninhibited proteolysis and oxidant injury to proceed. Adhesion molecules associated with both the neutrophils and vascular endothelium interact with each other and mediate the neutrophil adhesion to the endothelial surface. Two primary families of leukocyte-associated adhesion molecules have been identified and are called selectins and integrins. Selectins on neutrophils interact with carbohydrates on the endothelium and cause the neutrophil to slow and roll along the vascular wall. β_2 integrins (the heterodimers CD11a/CD18, CD11b/CD18, and CD11c/CD18) on the leukocyte then interact with endothelial surface adhesion molecules (eg, ICAM-1) and cause the neutrophil to stick firmly to the endothelium. Rolling is a necessary prerequisite before sticking or firm adherence can occur; thus, defects in either selectins or integrins will interfere with neutrophil adherence. Expression of integrins is 'upregulated' in animal models of ischemia/reperfusion and presumably in severe trauma or sepsis in humans. Monoclonal antibodies against leukocyte adhesion molecules, specifically against components of the CD11-CD18 leukocyte adhesion molecule complex, have shown dramatic effects in protection against many organ injuries in animal models of hemorrhagic shock or ischemia/reperfusion. The lung receives little or no protection, presumably because the CD11-CD18 complex is not involved in leukocyte adherence to pulmonary endothelium under these conditions. However, with significant protection to other organ injuries, particularly the gut and the liver, there may be a secondary effect in preventing or modifying subsequent pulmonary lung injury. Preparations are being made for controlled clinical trials of monoclonal antibodies against leukocyte adhesion molecules.

Cautions Regarding Anti-Inflammatory Therapy

Although the recent development of many anti-inflammatory agents has generated optimism regarding our ability to successfully intervene in the initiation and propagation of lung and other organ injury and thus to improve survival in these critically ill patients, several factors should cause us to pause and dampen this enthusiasm. For openers, we have 'heard this tune before.' Investigations of corticosteroids in animal models of conditions such as sepsis that result in lung and other organ injury indicated a beneficial effect. However, in human clinical investigations, corticosteroids have not been shown to have a protective effect in patients with trauma or sepsis, either in preventing ARDS and multiple organ failure or in reducing mortality. The clinical situation in humans is much more complicated than that in animal models, which might account for the difference in outcome between laboratory and clinical studies of corticosteroids. Humans developing ARDS have multiple etiologies; even when one tries to select a single etiology, considerable heterogeneity exists both in the underlying clinical condition and in host factors. Complications occurring during the clinical course may have a profound effect on outcome. Finally, the inflammatory cascade and process is so complicated that a single agent may not result in an important clinical effect. A redundancy of some of the inflammatory pathways exists such that if one mediator is blocked, the inflammatory process might continue through amplification of another pathway.

Clinical intervention trials may be carried out on patient populations that are not appropriate for the agents studied. This is a major concern of mine. Although cell and molecular biologic research has led

to the development of potential therapeutic agents earlier than expected, I believe our knowledge of the inflammatory injury process in patients has lagged behind—in part because of a relative paucity of funding for clinical studies. Therefore, little is known about the sequence and timing of the various steps in inflammatory organ injury and the clinical circumstances that affect these variables. Thus, it is entirely possible that study patients are selected in whom the agent being studied might have little potential effect, either because the mediator being inhibited is unlikely to be involved in injury in that patient or because the timing of the intervention is not optimal. In addition, dose or duration of administration resulting in maximal benefit might not be known. For these and other study-design reasons, a randomized controlled study of an agent with a potentially potent biologic effect might find that no clinical benefit occurred. Because these intervention studies are extremely expensive to carry out, one negative study might preclude further testing of such an agent.

Finally, inappropriate conclusions might be drawn by focusing on a single end point. I am particularly concerned about the emphasis on reduction in mortality as the sole end point in many of the studies. On the one hand, one could argue that if one of these interventions does not result in improvement in mortality, then little benefit has been derived. Countering this is the possibility that agents with beneficial physiologic or clinical effects but no improvement in mortality when studied individually, might result in mortality benefit when given in combination.

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Hudson Discussion

Dantzker: As I look at these cascades that everybody draws, my concern is can you block the top of the cascade? It's tough to go in and try to block individual pieces of it. It's going to be a job to try to mop up everything that's gone on after the cascade begins, and you're much more likely to begin to interfere with processes that are probably important. For example, as you already pointed out, if you stop white-cell adherence in patients in an ICU where we know there's always infection going on, you may well put them at risk for other problems. And also the cost will become enormous. I mean, if you have to give IL-1 receptor blockers, TNF antibodies, anti-adhesion molecule antibodies—you're likely to create a situation where an administrator will be standing at the emergency room door, trying to shoot anybody with sepsis who comes near the door because that type of patient is likely to bankrupt the hospital everytime he comes in. Isn't it disturbing that the endotoxin antibodies didn't work? If that's really the thing in sepsis that starts the cascade, and we load them up with antibodies, but it doesn't really make all that much difference, aren't you concerned that the rest of this stuff is going to be just a holding action?

Hudson: Well, first of all, I don't know that we know that monoclonal antibodies to endotoxin don't work.

Dantzker: It didn't work dramatically.

Hudson: Yeah, and it "doesn't work" in the studies that have been done if you take all comers with sepsis, which is what you have to do in order to include the group that you really want to study. As you know, one of the problems with all these studies is knowing who to include and at what time to include them. Often, I think the process is so far advanced (and I think that's the problem with sepsis) that a lot of the injury has already occurred. Now, with sepsis the premise is that it's an ongoing process, so we should be able to still show some effect. To answer you, yeah, I think it is disturbing, although I think, for example, the studies of monoclonal antibody against leukocyte adhesion molecules have shown dramatic effects if they can be given early enough after ischemia/reperfusion, including in a whole animal model of hemorrhagic shock.[1,2] Here the key would be getting to the patient at high risk early enough—because the effect is fairly transient, you probably only prevent the adhesion for a day, but that may be enough to have a significant effect on the injury that might result. So, I think there are lots of potential problems. I agree with you, and I think that's why we need good controlled trials, and they're going to be hard to do. One of the problems, in fact, in even doing the sort of study that Alan (Morris) was talking about with oxygen toxicity is that we're going to have patients on so many different agents. Everybody is going to be into a trial. We're now having to choose what we do want to study and which ones appear to be most important.

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Morris: I think we mislead ourselves when we say P_{O_2} improves or compliance improves. As a result of the profound decrease in cardiac output, an ARDS patient with cardiac arrest may have a P_{O_2} go from 53 to 200. If someone says, "The patient's P_{O_2} has improved," there's an inherent potential to mislead ourselves. I highly recommend that we say the P_{O_2} increased—not that it improved. We know in some circumstances the P_{O_2} can increase when the patient is succumbing. The problem, psychologically, is that if the P_{O_2} is improved then everyone (and I certainly figure among them) naturally assumes that the patient is improving. My second comment is that in this list you gave us I counted at least

9 variables dealing with epithelial injury and at least 8 variables dealing with endothelial injury. We know that the epithelium and the endothelium can interact, so whatever you find out about how the epithelium behaves independently may or may not be an appropriate descriptor of how it will behave when it's in fact adjacent to an endothelial cell. We know now that a mediator release can, in fact, be a function of multiple functions of different cells. Some cells can provide precursors to other cells and produce the ultimate mediator, which may, in fact, have a biological effect of interest. I would just remind us all that if we had a problem that had 9 variables, we would have to generate 9 simultaneous equations to generate the unique solution. If we had 18 variables, we would need 18 simultaneous equations. I won't take the argument any further but just point out that this is quite an impressive challenge. My last comment has to do with, I think, one of the most important things you said—the difficulty of doing clinical trials and the problems posed by multicentered trials that carry with them variations in behavior at different centers. One response to that would be to say that we can't do clinical trials adequately to answer the questions, and therefore we should deal with surrogate variables and do our own independent work in smaller numbers. Another response might be to address how we can deal with the variation among centers and enable all of them to take advantage of the power that comes from a well-conducted multicenter trial. I'd like to focus on that.

Hudson: I agree with that, and I favor the latter approach. I think that smaller studies aren't going to give the answers and that we need to have better-conducted multicenter trials.

Cerra: I have a question about the surfactant studies. I'm somewhat bothered that mortality was reported as an outcome that was statistically significant. Just based on what was said, the statistical power is not there. If I understood the surfactant data you presented, there are 4 or 5 different groups with very small numbers in each group. I'm just making the plea again that when data are reported, they be reported in a way that has some meaning. That's not to say that as a part of a Phase-I trial that data should be ignored . . .

Hudson: Well, it hasn't been reported yet (Oct 1992), so . . .

Cerra: Good, I had the impression that it had been published.

Hudson: No, it hasn't been published. Neither of these studies have been published. I think the surprising thing is that there appears to be some sort of trend in mortality.

Cerra: It's certainly an important Phase-I trial that needs to be followed up; however, it is not a primary outcome analysis. Second point, to get back to the point you made, which is the balanced hypothesis approach to the modulation of inflammation, which I happen to agree with 100%. It gets into all these issues of what to use when, and how to sequence them, and what are we going to do, and I just want to mention one more and that has to do with nitric oxide. Unquestionably it's a potent vasodilator and metabolic regulator, and balance is important. If you look at Simmons's most recent article in *Science*, it's probably the agent that mediates the myocardial depression in this so-called sepsis syndrome.[1] Too much nitric oxide is hepatotoxic (causing hepatonecrosis) and limits electron transport at the cytochrome level. So we're back on the same issue. Again, say in the study of nitric oxide inhalation, it's important that we look not only at patient disease-related outcomes but also at patient-related outcomes. What happens to organ failure? What happens to mortality? What happens to length of stay?

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Wood: Len, when you look at the 15 mediators or antagonists that are being studied and see too few patients to evaluate all these agents in your own center or in other centers, is there a way out of this? Or is it possible that the ARDS mortality is now low enough when effective supportive care is carried out that there aren't enough patients to go for that last fraction who would have their morbidity and mortality reduced if there were a specific therapy? There not being one, we're riding off in many different directions because the exact cause isn't clear and because the solution would require a super scientific centre of research (SCOR). SCORs have been going on exactly this topic, as you know, for years; your analysis implies that we need more centers enrolled in a super SCOR. This is a more organized approach to each of these agents with proper tiering and good design, that requires a lot more investigational funds from a central governing agency than are currently available.

Hudson: The sort of approach you propose has been suggested to NIH, and they are actually considering that there be some sort of approach like this. A central group of investigators would look at different proposals and decide which are the ones that appear to be most promising—because you can't study everything. Right now, that's always being driven by the companies, more than being a very logical decision; they approach certain clinical investigators. If you're approached, then you consider doing

that study. But there may be a priority, at least from what we know about preliminary data, to study certain agents over others as being most promising, both theoretically and from preliminary animal model data. I think we probably do need a more centralized approach. Whether that's going to be possible, in terms of funding, I'm not sure.

Wood: Many of your slides were addressing the acute lung injury in ARDS, and you arrived at modifiers of alveolar inflammation with the caveat "and systemic inflammation"—because the interleukin receptor antagonist (IL-Ra), the tumor necrosis factor (TNF) antibodies . . .

Hudson: Most of them are actually systemic. It's the other way around.

Wood: That is my point—these are looking at sepsis. And that may be fair enough, if we accept that inflammatory mechanisms of sepsis are responsible for what we are talking about—oxygenation failure in the critically ill patient. If that's not what we mean, then finding and treating the mediators of sepsis may not influence the treatment of acute lung injury. But we so often lump together the acute lung injury ARDS with sepsis in a lot of our conversations, and this talk was one of them.

Hudson: Yeah, and I agree with your implication that really, it's multiple organ failure and systemic inflammation, for the most part, that we're trying to prevent with most of these agents.

Cerra: Len, you might comment on one other thing, and that's the precedent that may have been set with the test chess trial, for HA-1A. It seems they've gone from an efficacy trial to a demand-for-effectiveness trial, which is essentially what the chess trial is. And if that's the standard they're going to hold all these studies to, then after you finish your efficacy trial you have to go to an effectiveness trial (broad-based, including community hospitals, and small hospitals, and large hospitals, in addition to university centers) then we have a whole other problem to deal with. And I wholeheartedly support your concept of some kind of central clearinghouse for the coordination of these big multicenter trials.

Stoller: Let me just follow up on the comment about the logistic difficulties of conducting multiple-agent studies. Like your center, ours is inundated by multiple sponsors to participate in multiple drug evaluations. The other trend is the fact that some of these agents may act additively. The question is, Who will support and sponsor multiple-agent evaluations when each pharmacologic sponsor is promoting his or her own product? I really feel this will be a challenge over the next 10 years, trying to organize a systematic approach and perhaps getting back to central governmental funding.

Morris: I'm a little concerned by this central agency concept because it conveys to me an image that carries significant potential for abuse and inappropriate control. Although central direction may be appropriate, perhaps from you, but not from a functionary, particularly not the person who talks about what we can or can't do based on a P_{O_2} level from a couple of years ago. But, I think the issue is not so much whether and who does what centrally, but has to do in large part with how we in the medical community view ourselves and what paradigm we use as a guide to how we interact with patients. It appears to me that for generations of medical training, the paradigm of the independent physician going to the bedside, interacting independently with the individual patients, putting all data together, and coming up with the best solution has driven everything. And that has led—this is, once again, meant to be observational and not critical, because I participated in that paradigm as intensively as anybody else—to a number of things that have a kind of humorous element. You know how you define where the sickest patients in the world happen to be? Who has the sickest ICU patients? They exist in the center you happen to be visiting, as a visiting professor. Everybody can tell you why *their* patients are sicker than the patients who were just published in a paper in the *New England Journal of Medicine*. You know where one of the best approaches to patient care occurs? It's in the ICU you happen to be visiting as a visiting professor because the director of that ICU corrected that thing that bugged him as a Fellow in training. Now he's convinced that he has, in fact, made progress. The perception that many of us have—that we're not part of the same business, that we're a little different and different enough so that Larry Wood's results really don't pertain to what we're doing—comes from a paradigm, which I think should be reexamined.

Hudson: What's the alternative?

Morris: Let's talk about that this afternoon.

Hudson: That's not fair . . . I think Larry (Wood) has already pointed out that somebody has to decide. Somebody has to make the decision.

Morris: Yeah, I think the key is that some*bodies* have to make the decision. I think the solutions are much more likely to be forthcoming if we as a community can get together and make the decisions. I don't think they're going to be forthcoming if some*body* makes the decisions.

Hudson: But the problem is whether there are data to make those decisions? For example, just what we talked about this morning, O_2 toxicity.

Morris: It all depends on how you formulate the question. Right?

Hudson: The answer's no.

Morris: Look, if I told you there was effective therapy for preventing long-bone fracture in automobile accidents, would you want to use it? Of course. What if I told you the effective therapy was the imposition of a 40-ton metal beam between the vehicle and the accident victim, and I told you it always works in every experimental model in which we've tried it. When we put this 40-ton beam between the vehicle and the accident, we prevent the problems—we have no ARDS, we have no multiple-organ failure, we have no broken bones. And then we went out and tried to sell you in the medical community, and it turned out that several of us lugged these beams around, and after we came upon accidents, we threw the beams near patients and it didn't work! But we were convinced they worked because we had appropriate experimental evidence that they were always effective. You know our conviction and prejudice that they worked would continue to drive us to develop new ways to throw beams at the patients after they were injured or arrived in the emergency room. It's our perceptions of the questions that in large part determine what we do. To get back to your question now, if you mean by the question, "Can we as a group decide what is right?", then the answer is "No." I could read the Bible to you and we could begin to talk about right and wrong, but if we want to decide what's right, the answer is, we can't. I mean, the truth is an elusive concept, isn't it? But I think if we got together and said, "Well, what is reasonable?" Given the information in the literature, is it reasonable to throw beams at the patients after they've been run over? You know we might decide it isn't. Given the information in the literature, I think we could come up with a reasonable approach, and a reasonable, standardized approach constitutes a platform from which improvements in performance can be effected.

Hudson: It doesn't unless it's accepted as being right, which is often the case. We've come up with a number of guidelines to therapy, and then what I find is pretty soon I'm being told by somebody that this is the way it *has* to be done. There's no variation from that to take into account other variables that should be accounted for. They're quoting these as being absolute, when I know that they're not since I helped make them up!

Morris: If you present guidelines, and Dantzker and I accept those guidelines and say, "This is reasonable. It's a good reflection of the information available." That could constitute, not necessarily an absolutist approach (an exclusionary absolutist approach in medical practice precludes any variation in the future) but rather the control arm of trial. In other words, you made reasonable guidelines, and Larry Wood comes over and says, "Yeah. You know, this particular piece of information suggests that if we give nitric oxide, we will in fact induce favorable changes." Well, we've the makings of a controlled trial. We've the guidelines, which constitute one group, and then the guidelines modified by the investigational agent, which constitutes another group. What isn't possible to do, in my opinion, is to have 14 different groups, using 27 different elements, in unpredictable and unspecified ways, and hope that somehow it's all going to even out in the wash. We can come back to that—what kinds of studies might make it easier to even out. If you came up with a guideline, chances are excellent I would use it. I respect you and I think you have a better grasp of this thing than I do, and I'd do it. What's the alternative? I can tell you what the argument was that I used—in fact I probably told you this before. When we first made our protocols in 1985-86, there were 14 of us around the table, at the end of one of these 2.5- to 3-hour sessions, with one person arguing that we need higher F_{IO_2} and lower PEEP, another arguing that we need lower F_{IO_2} and higher PEEP, another saying we should change every 2 hours, and another every 6 hours, another let's go up by 5, another let's go up by 2. I turned to everybody (most of whom were my students, so I actually had a real advantage) and I said, "You know, we all have different styles. Some of us are more afraid of oxygen. Some of us are more afraid of pressures. Some of us are more afraid of fast and slow changes. The only thing we have in common is that almost all of our patients die. So, since almost all of our patients die anyway (you know these were ECMO criteria for ARDS patients who at that time had a 91% mortality rate), why don't we just pick *a* way, and try and see if we can make some progress from a standard therapeutic platform." I think that argument is an important one to consider. Now, obviously, not all of our patients died of sepsis, and not all of our patients with ARDS died—about 50% for the overall group. The important thing is that 50% mortality for a 27-year-old mother of two is harrowing. These are patients who have a smaller chance of getting out of the hospital than people who come in with a diagnosis of malignant melanoma.

Wood: There's one other thing that David (Dantzker) mentioned earlier. I'm not exactly sure how he meant it, but the antibody to endotoxin (HA-1A) was a really interesting economic problem. When it looked like it

was going to be released by the FDA, the administrators in our hospital went into a panic because of what it would cost if HA-1A were used for septic shock as broad-spectrum antibiotics are appropriately used in septic patients. If HA-1A were used that way at a nonreimbursable cost of $7,000/patient, there was an easy calculation extrapolated from antibiotic use that the hospital would go bankrupt if we didn't have some kind of gatekeeping. Then we got into a major gatekeeping exercise.

Hudson: The cost of the drug was higher than the DRG for the condition. Then I found people at some hospitals in our area interpreting the data on that basis, rather than on whether they really felt that it showed a benefit or not. They tried to lobby because they wanted to *not* use it—that everybody shouldn't use it. I think you're absolutely right. Right now, it's an enormous problem not just for HA-1A, but it's going to be a problem with several of the agents. Several of them are projected to be in the same price range as HA-1A.

Dantzker: Let me just make one comment about the reduction of clinical trials. I sit on a clinical trial study section of the NHLBI. I've seen no clinical trials come through from the lung or critical care community. Most of the trials in critical care are being driven by the drug companies and not by the scientific community. Trials of certain agents, like ibuprofen, were funded by the NIH, but only after a lot of very hard work—because no drug company, obviously, was interested in using it. The aspirin trials would never have been done if we had depended upon drug companies to do them because there's no money in it.

Hudson: But there are some historical reasons that major clinical trials haven't been proposed to the NHLBI from the pulmonary community. The corticosteroid trial was turned down. The ibuprofen study was turned down after it initially had been approved, and it took a lot of effort to salvage it. I think there's been a lot of discouragement . . .

Dantzker: But there must be some reason why these trials are not being encouraged to come up to the clinical trial study section. I think that if we're to enlarge and grow as a group, especially in critical care, we need to start saying that that's just not allowable. We will not allow basic investigation, as important as it is, to totally monopolize the ability to run important multicenter clinical trials out from under the shadow of pharmaceutical companies who we all know drive them. No matter how hard they try, they drive them in a direction that is eventually going to be important for them.

Hudson: I also think that there should be some guidelines that we come up with for what's an acceptable clinical trial, regardless of who funds it, in order to be published. And we should put some teeth in the guideline, so that the companies virtually have to have investigator-controlled trials that are going to be reported even if they have negative results and that certain criteria need to be met before major journals will consider publishing them.

Therapeutic Manipulation of Oxygen Consumption and Carbon Dioxide Production in Acute Respiratory Failure

James K Stoller MD

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Introduction

One of the guiding principles for managing patients with sepsis and/or acute lung injury is to optimize oxygenation so as to match oxygen supply capability with oxygen consumption demands. Following this principle, much attention has been focused on enhancing oxygenation and oxygen delivery in patients with sepsis and/or acute lung injury.[1,2] In this review I consider alternate approaches to enhancing the balance between oxygen demand and supply and between carbon dioxide production and ventilation: strategies to decrease oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$). In reviewing these alternative approaches, I first describe the impact of hypothermia and of muscle paralysis as strategies to lessen $\dot{V}_{O_2}$. Second, I address strategies to alter $\dot{V}_{CO_2}$ by manipulating nutritional sources and the substrates of metabolism.

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Induced Hypothermia in the Management of Acute Respiratory Failure

Physiologic Effects of Hypothermia

As reviewed by Black et al,[3] Keamy and Hall,[4] and in Table 1,[3-5] hypothermia produces protean manifestations in many organ systems. Perhaps the most noteworthy effect, and that announced by headlines in newspapers when miraculous survivals follow prolonged cold water immersions,[6,7] is that hypothermia can lower metabolic demands and diminish oxygen requirements, permitting survival despite prolonged cardiopulmonary arrest.[8] Evidence that hypothermia can promote survival during stress comes from two disparate sources. First, by achieving core temperatures far below 10°C, hibernating animals survive long periods of time with-

Table 1. Organ System Effects of Hypothermia*

Metabolic/Endocrine
- ↓ Oxygen consumption ($\dot{V}_{O_2}$) (but ↑ $\dot{V}_{O_2}$ with shivering)
- ↓ Oxygen extraction ratio
- ↓ Cardiac output by ↓ heart rate
- Hyperglycemia (but ↓ plasma insulin)
- ↑ Catecholamines initially (to 31°C), then ↓ (to 29°C)

Respiratory
- Slow, shallow respirations
- Alpha stat pH (pH ↑ 0.015/°C)
- ↓ Lung compliance (?)

Cardiovascular
- Blood pressure and systemic vascular resistance preserved to 77°F (24°C), then ↓
- Central redistribution of volume
- Electrocardiographic changes
  - J (Osborn) wave below 91.4°F
  - Atrial fibrillation
  - Ventricular irritability
  - Atrioventricular block
  - Asystole

Central Nervous System
- Reversible coma
- ↓ Brain oxygen consumption

Renal
- ↓ Renal blood flow and glomerular filtration rate, but
- Diuresis ("cold diuresis"), with ↓ antidiuretic hormone (ADH) tubular response

Hematologic/Coagulation
- Granulocytopenia
- Thrombocytopenia and impaired platelet function

Gastrointestinal
- Ileus

*Adapted from References 3-5.

out nutrition or hydration. Second, advances in cardiac surgery and cardiopulmonary bypass perfusion permit routine survival when open heart surgery is conducted with deep hypothermia and extracorporeal perfusion.[9]

Many studies demonstrate that hypothermia is associated with decreased $\dot{V}_{O_2}$. For example, as reviewed in Table 2,[10-13] when shivering is controlled by muscle paralysis, cooling dogs to 30-32°C core is associated with a 27-45% decline in $\dot{V}_{O_2}$. In early studies of techniques for cardiopulmonary bypass, Bigelow et al[14] observed an almost linear reduction in $\dot{V}_{O_2}$ in dogs cooled to 18°C. Summarizing the relationship between reduced $\dot{V}_{O_2}$ and lowered body temperature as exponential, Willford et al[15] observed that $\dot{V}_{O_2}$ approximately halves with each 10°C drop in core temperature (ie, Q_{10}, the fall in $\dot{V}_{O_2}$ with each 10°C fall in temperature, equals 2, so that $\dot{V}_{O_2}$ falls by 7% per 1°C decrease).

Table 2. Impact of Hypothermia on Oxygen Consumption in Selected Series

Author (Date)	Model	Temperature	Decrease in $\dot{V}_{O_2}$ vs Normothermia
Gutierrez et al (1986)[10]	Dog	30.5°C	28%
Hershenson et al (1989)[11]	Dog	30°C	45%
Johnston et al (1989)[12]	Dog	31.9°C	27%
Morray & Pavlin (1990)[13]	Dog	29°C	36% (brief cooling) 42% (24-h cooling)

Although hypothermia invariably lowers $\dot{V}_{O_2}$ (when shivering is controlled) and lowered $\dot{V}_{O_2}$ is desirable to enhance matching of $\dot{V}_{O_2}$ with diminished oxygen supply, several other effects of hypothermia may cause impaired oxygen delivery to tissues (D_{O_2}) or impaired oxygenation.[3] The opposing effects of hypothermia that conspire against D_{O_2} could serve to vitiate the benefits of hypothermia (Table 3): (1) left-shifting of the oxyhemoglobin dissociation curve, which may cause diminished ability to unload oxygen to tissue (ie, lowered P_{50}); (2) impaired oxygen extraction by tissues by interrupting microcirculatory responses to local hypoxemia; (3) attenuation of hypoxic pulmonary vasoconstriction;[16] and (4) the granulocytopenia that frequently accompanies cooling.[17,18] This being so, careful assessment of hypothermia as treatment for acute lung injury requires understanding the net physiologic impact of these potentially opposing effects.

Animal Studies of Hypothermia

To examine the net impact of hypothermia on D_{O_2}, Willford et al[15] conducted a theoretical analysis of the effects of hypothermia, taking into account the effects of cooling to decrease $\dot{V}_{O_2}$ and tissue extraction of oxygen and also to increase oxygen solubility, pH, and avidity of hemoglobin's binding

Table 3. Hypothermia for Hypoxemic Acute Lung Injury: Pro and Con

Pro

Hypothermia decreases oxygen consumption.

Decreased oxygen consumption may be accompanied by preserved ability of tissues to extract oxygen.

Con

Hypothermia may be accompanied by impaired oxygen delivery to tissues, caused by

- mismatch of oxygen supply to demand at local tissues, as by vasoconstriction.
- increased blood viscosity and decreased RBC deformability.
- left-shift of oxyhemoglobin dissociation curve and decreased tissue unloading of oxygen.
- attenuation of hypoxic pulmonary vasoconstriction.

Granulocytopenia may impair defense against infection.

to oxygen. The theoretical analysis shows that under hypothermic conditions (core temperature 27°C) and with P_{aO_2} of 100 torr, anemia (hemoglobin = 7.5 g%, or 7.5 g/dL), and constant relative alkalinity of blood with cooling, a cardiac output of 50 mL · min^{-1} · kg^{-1} is associated with only a small margin of reserve before mixed venous saturation ($S_{\bar{v}O_2}$) is so low that oxygen demands cannot be met. A sensitivity analysis of factors influencing the mixed venous oxygen tension ($P_{\bar{v}O_2}$) shows that falls in $S_{\bar{v}O_2}$ are most sensitive (in decreasing order of magnitude of effect) to increasing $\dot{V}_{O_2}$, decreasing P_{50} of hemoglobin, decreasing cardiac output (C.O.), and decreasing hemoglobin. P_{aO_2} exerted less effect than the foregoing factors on $P_{\bar{v}O_2}$.

Beyond this theoretical analysis, several direct animal studies have considered the net effects of hypothermia in view of these potentially offsetting physiologic effects. First, with regard to the potentially deleterious effect of a left-shifted oxyhemoglobin dissociation curve on D_{O_2}, Schumacker et al[19] have shown that the level of systemic oxygen supply at which $\dot{V}_{O_2}$ becomes supply-dependent (the so-called critical D_{O_2}, or $D_{O_{2crit}}$) and the extraction ratio (defined as the arteriovenous oxygen content difference divided by the arterial oxygen content, or $C_{(a-\bar{v})O_2}/C_{aO_2}$) was the same with dogs transfused with low-P_{50} blood (ie, higher avidity of hemoglobin for oxygen) as with control animals. Based on these studies, the higher avidity of hemoglobin for oxygen at lower temperatures does not appear to be responsible for any impairment of D_{O_2}.

Other studies have examined the offsetting effects of decreased $\dot{V}_{O_2}$ versus possibly impaired D_{O_2} by considering the impact of cooling on tissue extraction ratio at $D_{O_{2crit}}$ (the so-called critical extraction ratio). A decreased critical extraction ratio during hypothermia indicates impaired ability to extract oxygen. As reviewed in Table 4,[10,11,20,21] results of available animal studies are mixed. Cain and Bradley[20] and Hershenson et al[11] have shown that extraction ratio at $D_{O_{2crit}}$ does decrease with hypothermia, and Schumacker et al[21] have shown a nonsignificant trend towards decreased critical extraction ratio in hypothermic dogs. In contrast, Gu-

Table 4. Effect of Hypothermia on Oxygen Delivery and Uptake

Author (Date)	Model Used	Temperature	Critical O_2 Supply ($D_{O_{2crit}}$)* (mL · min^{-1} · kg^{-1})	Extraction Ratio at $D_{O_{2crit}}$
Cain & Bradley (1983)[20]	Rat, hypoxic hypoxia†	34°C	22 vs 20 (38°C)	Lower at 34°C than at 38°C
Gutierrez et al (1986)[10]	Dog, hypoxic hypoxia	30.5°C	6.2 vs 8.5 (37.7°C)	0.47 vs 0.47
Schumacker et al (1987)[21]	Dog, hemorrhage	34°C	5.6 vs 7.4 (38°C)	0.65 vs 0.71 (38°C), trend but NS‡
Hershenson et al (1989)[11]	Dog, hypoxic hypoxia	30°C	11.4 vs 9.3 (38°C), no difference	0.42 vs 0.60 (38°C), $p < 0.05$

*Level of O_2 uptake at which O_2 uptake becomes supply-dependent.
†Hypoxic hypoxia indicates decreasing F_{IO_2} to decrease cardiac output and O_2 delivery.
‡NS = not significant.

tierrez et al[10] have shown that extraction ratios are preserved at hypothermic $D_{O_{2crit}}$. As discussed by Schumacker et al[21] and Gutierrez et al,[10] discordant conclusions from available studies may relate to differences in species and/or the experimental methods used to lower D_{O_2} (eg, hemorrhage vs lowering inspired oxygen tension, stagnant vs progressive hypoxia).

To the extent that hypothermia does impair tissue oxygen extraction at $D_{O_{2crit}}$, the observation that a lower P_{50} alone does not decrease the critical extraction ratio[19] favors a mechanism of impaired microcirculatory responses to tissue hypoxia or altered rheologic properties of blood. In support of the latter possibility, Hershenson et al[11] have shown that administering pentoxifylline, a drug that vasodilates and decreases blood viscosity, restores the critical extraction ratio in hypothermic dogs to normothermic values. Confirmation of these benefits of pentoxifylline in human hypothermic studies is not currently available.

To the extent that demonstrating clinical benefit requires supportive animal studies and clinical studies in humans, the dearth of available studies leaves uncertainty regarding the benefits of hypothermia in managing sepsis and/or acute lung injury. In an animal study of oleic acid-induced canine pulmonary edema, Johnston et al[12] have shown that hypothermia improves oxygen supply-demand balance by decreasing systemic oxygen demands without improving arterial oxygenation or D_{O_2}. Their conclusions seem to summarize current impressions and evidence about the clinical efficacy of hypothermia for human acute respiratory failure: "No studies have documented the therapeutic efficacy of hypothermia in improving patient survival with severe respiratory failure. Rather, hypothermia should be viewed as a temporary measure to maintain the balance of tissue oxygen and demand when conventional methods prove unsuccessful."[12]

Clinical Studies of Hypothermia for Acute Respiratory Failure

Human studies evaluating hypothermia in acute lung injury are summarized in Table 5.[22-25] Although several investigators suggest that hypothermia is widely employed as a "salvage" strategy when more conventional means to enhance oxygen have failed,[26,27] this impression of widespread use of hypothermia contrasts with the published experience, which is sparse in humans.

Furthermore, the only published controlled study of hypothermia in humans suggests that cooling is associated with poor overall survival rates. Specifically, in a retrospective study of 40 comatose children after freshwater near-drowning, Bohn et al[17] compared survival in patients managed with 2 different protocols: Group 1 (n = 24, seen in 1978-1980), managed with hypothermia to 30-33°C for 24-36 hours, high-dose barbiturates, hyperventilation, and paralysis vs Group 2 (n = 16, seen in 1980-1982), managed identically except without hypothermia.

Table 5. Hypothermia in Human Acute Lung Injury: Available Experience

Author (Date)	Patient Type (n)	Study Type	Regimen	Outcomes
Flachs et al (1977)[22]	ECMO* candidate (8)	Observational, no controls (letter)	34°C, paralysis, PEEP	Survival in 7/8
Gilston (1983)[23]	Pulmonary edema after upper airway edema (1)	Case report	34.5°C, paralysis	Survived, P_{aO_2} ↑ from 60 to 110 torr
Hurst et al (1985)[24]	ARDS after arrest (1)	Case report	33°C (core), paralysis, PEEP, HFJV	Survived
d'Empaire et al (1985)[25]	ARDS (6)	Observational, no controls (abstract)	35°C mean, paralysis	$C_{(a-\bar{v})O_2}$ ↑ by 0.55 mL/100 mL, detrimental by ↓ D_{O_2} more than $\dot{V}_{O_2}$

*ECMO = extracorporeal membrane oxygenation; PEEP = positive end-expiratory pressure; ARDS = adult respiratory distress syndrome; HFJV = high frequency jet ventilation; $C_{(a-\bar{v})O_2}$ = difference in arterial and venous oxygen content; D_{O_2} = tissue oxygen delivery; $\dot{V}_{O_2}$ = oxygen uptake.

Table 6. Effect of Muscle Paralysis on Oxygen Consumption: Selected Animal Studies

Author (Date)	Model	n	Paralysis	Findings
Muldoon & Theye (1969)[29]	Dog	5	Succinylcholine	$\dot{V}_{O_2}$ ↑ by 9% in first hour after succinylcholine; ↑ $\dot{V}_{O_2}$ ablated by pretreating with d-tubocurarine
Rurak & Gruber (1983)[30]	Fetal lamb	7	Gallamine to fetus	$\dot{V}_{O_2}$ ↓ by 17.2% in fetuses breathing before paralysis
Cameron et al (1986)[31]	Newborn lamb	12	d-tubocurarine or pancuronium	$\dot{V}_{O_2}$ ↓ by 35% (d-tubocurarine) and 50% (pancuronium), but only with hypoxic paralysis (not with normoxemic paralysis)

Mortality in Group 1 (managed *with* hypothermia) was higher (42% vs 19%) and was associated with more severe neutropenia, which may accompany hypothermia.[17,18]

Overall, the following conclusions regarding the role of hypothermia in managing acute respiratory failure seem apt. (1) Despite ample evidence that hypothermia lowers $\dot{V}_{O_2}$ and is associated with surprising survival after cold-water immersion and with extracorporeal perfusion, other effects of hypothermia suggest impaired D_{O_2}. Therefore, the effects of cooling need to be weighed to determine the clinical role of hypothermia. (2) Animal studies on the net oxygenation effect of hypothermia have produced mixed results, with some showing decreased tissue extraction ratios at $D_{O_{2crit}}$. (3) Despite recommendations by some authors, clinical studies of hypothermia in human acute lung injury (n = 4) are too few and the aggregate number of patients examined in these studies (n = 16) is too small to establish the efficacy of hypothermia as a "salvage" strategy when hypoxemia is profound. (4) The only available controlled study of hypothermia is a retrospective study[17] using nonconcurrent controls, but suggests that mortality is higher in patients managed with hypothermia, possibly related to infection complicating cold-related neutropenia.

Muscle Paralysis in the Management of Acute Respiratory Failure

As with hypothermia, the appeal of paralyzing patients with hypoxemia relates to the decrease in $\dot{V}_{O_2}$ that accompanies the skeletal muscle relaxation.[28-31] Specifically, to the extent that skeletal muscle has been estimated to contribute 30-40% of total $\dot{V}_{O_2}$[29] and that the respiratory muscles account for approximately 4% of $\dot{V}_{O_2}$ in normal patients (and up to 21% in malnourished COPD patients),[32] skeletal muscle paralysis offers the possibility of greatly reducing $\dot{V}_{O_2}$. Paralysis may be especially appealing for managing the uncontrolled skeletal muscle contractions that accompany shivering, which may increase $\dot{V}_{O_2}$ four-to-fivefold.[14,33-35]

As reviewed in Table 6, animal studies confirm that nondepolarizing paralytic agents such as gallamine, d-tubocurarine, and pancuronium can decrease $\dot{V}_{O_2}$ by up to 50%.[29-31] In contrast, by causing fasciculations, depolarizing paralytic agents like succinylcholine can increase $\dot{V}_{O_2}$, an effect that is ablated by preventing fasciculations with nondepolarizing paralytics.[29] Not surprisingly, the decrement in resting $\dot{V}_{O_2}$ following paralysis with nondepolarizing drugs is greatest in those animals with baseline skeletal muscular activity. In the study by Rurak and Gruber,[30] $\dot{V}_{O_2}$ in fetal lambs following gallamine decreased by 17.2% in animals with baseline breathing, but did not decrease in lambs that were not breathing before paralysis. Similarly, Palmisano et al[36] have shown that pancuronium given to normoxic infants after cardiac surgery decreased $\dot{V}_{O_2}$ by 13% in moving children but did not decrease $\dot{V}_{O_2}$ in children without baseline breathing or movement of the extremities.

Despite the appeal of using paralysis to decrease $\dot{V}_{O_2}$, relatively little attention has been given to the effects of muscle paralysis on $\dot{V}_{O_2}$ and oxygen utilization in clinical settings. Table 7 summarizes the 6 available clinical studies,[28,37-41] which examined a total of 117 patients, all but 10 of whom were newborns. Two studies[40,41] (10 patients total) con-

Table 7. Improved Oxygenation After Muscle Paralysis: Available Clinical Series

Author (Date)	n	Patient Type (Drug)	Oxygenation		Impact of Paralysis
			Before	After	
Henry et al (1979)[37]	10	Newborns (pancuronium)	Mean 62 torr	Mean 144 torr	↓ Mortality in paralyzed group (20% vs 73% in historical controls)
Stark et al (1979)[28]	27	Newborns	12/27 (44%) with $P_{(A-a)O_2} > 300$ torr show ↓ $P_{(A-a)O_2}$ of ≥ 100 torr		Not due to ↑ $\dot{V}_E$
Crone & Favorito (1980)[38]	20	Premature newborns with RDS	47.9 torr	101.8 torr	Due to better V/Q, not ↑ $\dot{V}_E$
Pollitzer et al (1981)[39]	50 (RCT*)	Newborns with RDS (pancuronium)	No change in P_{aO_2} or F_{IO_2} needed		Pancuronium associated with shortened duration of supplemental O_2
Bishop (1984)[40]	9	Adults (ARDS 5, pneumonia 3, flail chest 1) (pancuronium)	No change in P_{aO_2} or $\dot{Q}_{sp}/\dot{Q}_t$ after		$\dot{V}_{O_2}$ ↓ in 8/9 patients
Coggeshall et al (1985)[41]	1	27 WF ARDS (pancuronium)	65% saturation	90% saturation	↑ S_{pO_2} ↓ $\dot{V}_{O_2}$ (from 146 to 100 mL/min)

*RCT = randomized controlled trial.

sidered the effects of muscle paralysis on oxygenation in adults, 6 of whom had the adult respiratory distress syndrome.

Though most studies demonstrated a decrease in $\dot{V}_{O_2}$ associated with nondepolarizing paralytic agents, results in studies were mixed. Crone and Favorito[38] described a mean rise in P_{aO_2} from 47.9 to 101.8 torr following pancuronium in 20 newborns with respiratory distress syndrome. Henry et al[37] observed improved P_{aO_2} following metocurine in all 10 newborns for whom baseline and follow-up blood gases were available (mean 62 torr to 144 torr, using the same inspired oxygen concentration). In slight contrast, Stark et al[28] observed improved alveolar-arterial oxygen gradients (by ≥ 100 torr) in only some (12/27, or 44%) of newborns given pancuronium. Notably, these 12 responders could not be distinguished from the 15 nonresponders by birthweight, gestational age, or diagnosis, and were not observed to have more skeletal muscle movement at baseline than nonresponders. Finally, in the only available controlled trial of paralysis for infants with respiratory distress syndrome, Pollitzer et al[39] observed no decrement in inspired oxygen requirements following paralysis with pancuronium. Mortality rates were low overall (6%), and did not differ significantly between compared groups (8.3% pancuronium vs 3.8% controls). Similarly, no difference in the rate of barotrauma (pneumothorax and/or interstitial emphysema) was seen between the compared groups (12.5% pancuronium vs 15.4% controls).

As with the experience in newborns, studies of paralysis for enhancing oxygenation in adults[40,41] have provided mixed conclusions based on a small reported experience (10 patients total). In a single case report, Coggleshall, Marini, and Newman[41] described a 27-year-old woman with adult respiratory distress syndrome (ARDS) whose arterial saturation increased rapidly and repeatedly after paralysis with pancuronium (ie, from 65% to 90% saturation). $\dot{V}_{O_2}$ fell from 146 to 100 mL/min with concomitant small increases in $P_{\bar{v}O_2}$ (31 to 33 torr) despite a fall in C.O. (5.5 to 4.0 L/min). In addition to the observed decrease in $\dot{V}_{O_2}$, other possible ex-

planations for the enhanced oxygenation in this patient included (1) decreased venous admixture accompanying decreased C.O. in ARDS, and (2) enhanced ventilation-perfusion matching, perhaps accomplished by increasing functional residual capacity by eliminating expiratory muscle contraction that might encroach on expiratory reserve volume.

In contrast to the experience in this single adult patient, Bishop[40] described 9 ventilated adults (5 with ARDS, 3 with bacterial pneumonia, and 1 with trauma and flail chest) whose gas exchange and hemodynamics were reassessed 10 minutes after paralysis with pancuronium. Hemodynamic effects of muscle relaxation in these patients included increased heart rate with decreased stroke volume (but no concomitant change in blood pressure or C.O.), increased systemic vascular resistance (987 to 1,221 dyne · s · cm^{-5}, p = 0.04), increased pulmonary vascular resistance (163 to 205 dyne · s · cm^{-5}, p = 0.004), and increased mean pulmonary artery pressures (28 to 31 torr, p = 0.01). Muscle relaxation was associated with decreased $\dot{V}_{O_2}$ in 8 of 9 patients (mean decrease from 435 to 367 mL/min) but with no significant changes in P_{aO_2} or fraction of venous admixture. Bishop concluded that muscle relaxation seems most suitable to lower $\dot{V}_{O_2}$ when skeletal muscle oxygen consumption is high, but that the potentially adverse hemodynamic sequelae must be considered in using muscle relaxation. Reasons for discordance between lack of improvement in oxygenation in these 9 patients and the dramatic improvement in saturation observed by Coggleshall et al[41] are not apparent from the available reports.

Overall, although muscle paralysis is used routinely in anesthesia and critical care, organized studies of the hemodynamic and gas exchange effects of skeletal muscle relaxation are sparse. Based on this review of the available literature, the following conclusions about the efficacy of muscle paralysis in managing hypoxemic patients seem apt. (1) From limited available data, paralysis with nondepolarizing drugs can lessen $\dot{V}_{O_2}$, presumably by decreasing skeletal and respiratory muscle function. (2) The effects of paralysis on oxygenation are variable, with improved oxygen tension and alveolar-arterial oxygen gradient frequently but not uniformly observed. (3) Paralysis may be associated with unfavorable hemodynamic effects in patients with hypoxic respiratory failure (ie, increased pulmonary vascular resistance and increased systemic vascular resistance without increased C.O.), though the clinical impact of these changes may be small. (4) Current data are inadequate to support a survival advantage with paralysis or a clear-cut advantage for gas exchange. Pending further clarification of the clinical role of skeletal muscle paralysis, the observation that oxygenation can be improved with skeletal muscle relaxation suggests that paralysis with nondepolarizing drugs can be used to treat dyssynchrony with the ventilator and as a "salvage" attempt in individual hypoxic patients.

Impact of Nutrition and Metabolic Substrates on Gas Exchange

Unlike hypothermia and paralysis, which have been recommended by some investigators when hypoxemia is seriously threatening, nutritional manipulation has been of greatest interest for altering $\dot{V}_{CO_2}$ and ventilation.[42-44]

The Bohr equation shows that the P_{aCO_2} is proportional to the rate of CO_2 production and inversely related to alveolar ventilation. $\dot{V}_{CO_2}$, in turn, is influenced by temperature (such that P_{aCO_2} rises by 13% per °C rise above normal[45]), by the metabolic substrate for energy production (ie, fat vs carbohydrates), and by whether ingested calories are used for energy generation (ie, glycolysis or lipolysis) or energy storage (ie, lipogenesis or glycogenesis).[46] When calories are used to generate energy, $\dot{V}_{CO_2}$ is dictated by the available metabolic pathways, which depend on the metabolic substrate and, in the case of glucose, whether metabolism is aerobic or anaerobic. When glucose is oxidized via the citric acid cycle, metabolism is summarized as

$$\text{Glucose} + 6\ O_2 \rightarrow 6\ O_2 + 6\ H_2O, \qquad [1]$$

generating 686 kcal/mole.

Aerobic glycolysis produces 6 molecules of CO_2 for 6 molecules of O_2 consumed, yielding a respiratory quotient (or RQ, the ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$) of 1.0.[46]

In contrast, when fat is the metabolic substrate to produce energy, the metabolic equation resembles that for palmitic acid:

$$\text{Palmitic acid} + 23\ O_2 \rightarrow 16\ CO_2 + 16\ H_2O, \quad [2]$$

yielding a respiratory quotient of 16/23, or 0.70.

Finally, the RQ will vary with the state of nutritional repletion. In hypermetabolic patients in whom supplied calories are being metabolized, lipogenesis is minimal and the RQ reflects the caloric source supplied. In contrast, in nutritionally replete patients, supplied calories may cause glucose to be stored as glycogen or fat. The process of lipogenesis is associated with an RQ of 6 to 10,[46] depending on the lipid produced.

$$\text{RQ of glucose to tri-palmitin } (C_{51}H_{110}O_6) = 9.6. \quad [3]$$

$$\text{RQ of glucose to tri-stearin } (C_{57}H_{110}O_6) = 10.8. \quad [4]$$

$$\text{RQ of glucose to tri-olein } (C_{57}H_{104}O_6) = 6.74. \quad [5]$$

Thus, carbohydrate intake that far exceeds resting energy expenditure (REE) can cause the RQ to approach 10, with consequent increases in $\dot{V}_{CO_2}$ and possibly P_{aCO_2} if minute ventilation cannot keep pace with increased $\dot{V}_{CO_2}$.[47]

In the context of the Bohr equation, two aspects of the diet appear to influence the rate of $\dot{V}_{CO_2}$: (1) total calories administered and (2) the mix of carbohydrates vs fat as calorie sources.

That excess total calories predispose to hypercapnia has been shown by several investigators. For example, Van Den Berg and Stam[48] examined $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in 9 mechanically ventilated patients alternately given identical enteral nutrition regimens in different total amounts, 1.5 × REE (REE, mean 2,555 kcal/day) vs 2.0 × REE (mean 3,710 kcal/day). $\dot{V}_{CO_2}$ and RQ were higher when patients received more calories and resulted in hypercapnia in 4 of the patients during weaning (mean P_{aCO_2} increased from 42.4 torr to 50.1 torr). Similarly, Talpers et al[49] administered fixed-composition total parenteral nutrition (TPN, with 60% carbohydrate, 20% fat, 20% protein) to 10 mechanically ventilated patients in 3 different amounts of total calories: 1.0 × REE, 1.5 × REE, 2.0 × REE. Mean $\dot{V}_{CO_2}$ increased progressively from 181 mL/min to 211 mL/min to 244 mL/min in the compared groups, but failure to standardize and preserve minute ventilation rates precluded reliable comparison of patients' carbon dioxide tensions.

Some study results,[49,50] although disputed, also show that diets high in carbohydrates can predispose to hypercapnia even when total calories are not excessive. For example, Sue et al[50] have shown that $\dot{V}_{CO_2}$ varies between two isocaloric diets (both 1.3 × basal metabolic rate) given to 8 normal subjects, one diet containing 70% calories from carbohydrates and the other containing 10% of calories from carbohydrates. With a high carbohydrate diet at rest, $\dot{V}_{CO_2}$ was significantly higher (290 mL/min) than with a low carbohydrate diet (240 mL/min) without concomitant changes in $\dot{V}_{O_2}$ or minute ventilation.

Overall, it appears that administering excessive calories poses the greatest risk for the development of hypercapnia, and that with diets providing recommended amounts of total calories (1.25 to 1.3 × REE), the effect of varying the proportion of dietary carbohydrate vs fat on $\dot{V}_{CO_2}$ is more variable.[48,50] Finally, the risk of TPN-associated hypercapnia increases as minute ventilation decreases.[47]

As summarized in Table 8, administering excess calories and/or excess carbohydrates can cause hypercapnia and impair weaning of mechanically ven-

Table 8. Diet-Induced Hypercapnia: Selected Series

Author (Date)	n	Patients	kcal/day as CHO*	Ventilation
Covelli et al (1981)[51]	3	Adults post-op	Up to 2,500 kcal/day	P_{aCO_2} ↑ as CHO ↑
Dark et al (1985)[52]	2	ARDS	4,284 and 2,550 CHO kcal/day	P_{CO_2} ↑ to 53 and 52 torr
Herve et al (1985)[47]	6	COPD on MV	Up to 2,500 kcal/day	Mean P_{aCO_2} 60 torr

*CHO = carbohydrate.

tilated patients.[47,51,52] For example, Covelli et al[51] observed 3 patients with underlying obstructive or restrictive lung disease whose hypercapnia (zenith P_{aCO_2} 93 torr) developed while they were receiving up to 2,500 carbohydrate kcal/day and resolved with reduction of total calories to 850-1,500 carbohydrate kcal/day. Similarly, Dark et al[52] reported two young, previously healthy patients who developed ARDS and went on to experience hypercapnia (increasing P_{aCO_2} from 36 to 53 torr and from 42 to 52 torr, respectively) while receiving up to 5,400 kcal/day in total calories (4,084 kcal/day as carbohydrates). $\dot{V}_{CO_2}$ had increased to 500 mL/min in one patient and was associated with hypercapnia despite a minute ventilation of 22 L/min. In both of these patients, hypercapnia from overfeeding precluded weaning, which was ultimately successful only after total calories administered were reduced.

In summary, although adequate nutrition of mechanically ventilated patients is essential to avoid the increased debilitation associated with malnourishment, indiscriminate administration of excessive calories, especially as carbohydrate calories, can increase carbon dioxide production and precipitate ventilatory failure in patients with limited ventilatory reserve.

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Stoller Discussion

Wood: I want to make a couple of comments to put a lot of your remarks regarding oxygen consumption into the context in which I see them. The most effective ways of reducing oxygen consumption are to reduce the work of breathing and other muscle activity. The second most important is to normalize increased body temperature. On the first point, there is, by our review as well as yours, not a great deal of data about what the oxygen cost of breathing is in the critically ill, oxygenation-failure patient—usually one with ARDS or pulmonary edema. Dr Manthous in our group has some preliminary data,[1] and some of you may also be doing this. If you're not doing it, there are a couple of practicalities here—measuring oxygen consumption by a metabolic cart method in patients requiring cardiopulmonary resuscitation just before intubation and again just after muscle relaxation is an awkward procedure. It requires a competent airway-control person to hook the cart up effectively to the patient whose $\dot{V}_{O_2}$ is being measured while ensuring an adequate airway and ventilation. The kinds of data that come out of that surprised us at first. What we did to simplify things was to intubate and ventilate the patients with assist-control (AC) while measuring $\dot{V}_{O_2}$; then we allowed the patient to breathe spontaneously on the CPAP mode for a brief period to repeat $\dot{V}_{O_2}$ before we instituted (with their permission) muscle relaxation (MR); and then we measured $\dot{V}_{O_2}$ again. We took the O_2 cost of breathing to be the difference in $\dot{V}_{O_2}$ between CPAP and MR. Out of the first 5 patients that Dr Manthous studied before I came to this meeting, the reduction in the oxygen consumption was as much as 200 mL/min, and the O_2 cost of breathing averaged more than one third of $\dot{V}_{O_2}$, a number very much larger than I had imagined, but not inconsistent with the data that Roussos's group published in hypoperfused dogs.[2,3] Dr Manthous's preliminary data[1] also note that AC ventilation in sedated patients sometimes eliminated the O_2 cost of breathing, but AC sometimes actually increased $\dot{V}_{O_2}$ compared to CPAP. I emphasize that reducing the $\dot{V}_{O_2}$ won't help when the patient has an adequate delivery of oxygen, but it may matter in the patient with oxygenation failure in whom there are some limitations on maintaining adequate cardiac output, arterial oxygen saturation, or hemoglobin concentration. So I reduce $\dot{V}_{O_2}$ as a complementary therapy to raising D_{O_2} in virtually all patients who have a supply/consumption problem.

Once they're paralyzed, I can turn to the temperature-related O_2 consumption. I interpret all the data that you reviewed from several studies (including Gutierrez and Dantzker, and Schumacker with our group) as saying the following thing—that inducing hypothermia doesn't create a major problem with extraction.[4,5] You properly said that Schumacker et al is the one study that showed there was an extraction problem, and, yet, when we looked carefully at our data in this context, we found a 'diddley-squat' problem only when we rendered the animal hypothermic.[4] Accordingly, when we[4] and others[5] lower the $\dot{V}_{O_2}$ by lowering body temperature from 41°C to 37°C, we decrease the amount of O_2 delivery that is needed to maintain oxygen consumption. We don't render our patients hypothermic. What we do is when they're hyperthermic, we cool them to normal body temperature if they are anaerobic or close to the limits of aerobic metabolism.[6] In other words, don't make them hypothermic because the same Schumacker study that you quoted[4] actually used a hyperthermic group, with 41°C, which many of our pyrexic patients approach. And early on, we will lower their temperature with care to make sure that they're not shivering. That point is an amazing one to me—how often physicians will apply a cooling blanket to a patient for purposes of lowering temperature, and even for purposes of lowering metabolic demand, without recognizing that $\dot{V}_{O_2}$ goes way up if the patient is cooled without muscle relaxation. I believe one of your papers showed a 200 mL/min increase, and that's what we see.

So those are the sequential interventions that I institute to lower the oxygen consumption—decreasing the muscle activity, some of which is respiratory, then decreasing the temperature from hyperthermia to normal. The last point is on the edge of salvage therapy for the really tough, hypoxic patient. If there is no extraction defect induced by left-shifting the oxyhemoglobin dissociation curve, either by hypothermia[4] or by alkalemia to lower P_{50},[6] then there is a second benefit of lowering body temperature in that there is more arterial O_2 loading for a given $P_{O_2}/F_{I_{O_2}}$. What you end up being able to do is not only lower the $\dot{V}_{O_2}$ with the temperature down but also get more arterial saturation by left-shifting the oxyhemoglobin dissociation curve. But I regard that as sort of pushing the fringes. One last comment—those first two measures included muscle relaxation, and muscle relaxation is increasingly being associated with protracted neuromuscular defects;[7] so, we're cautious and not cavalier when we use paralyzing agents. That's why I said when I have a tough supply-consumption relationship, I'll use it early and I'll get out early—just as soon as we can get some of the things corrected that are causing the oxygenation failure.

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Pierson: It's my observation in our ICU that the most common mechanism or circumstance leading to the initiation of paralysis is that the patient is desaturated, as indicated solely by a change on the pulse oximeter. I think and argue that that probably results in perhaps half of all of our ARDS patients, at one time or another, being paralyzed. How would you choose when to go ahead and paralyze someone?

Wood: That's a really good point. My observation in our unit is that the commonest cause for paralyzing a patient with ARDS or other forms of acute hypoxic respiratory failure is that the resident writing the orders finds the patient is "bucking the ventilator." Under those circumstances, I prefer to adjust the ventilator to make the patient comfortable rather than sedate and paralyze the patient. Often, turning up the tidal volume from my usual low value, or turning up the flowrate (a flow that is too low is a common cause of increased work of breathing on the ventilator) will comfort the patient. If that doesn't work, then I'll use vocal anesthesia and then some sedation with anxiolytic drugs, before I get to muscle relaxation. If, on the other hand, the patient is on the edge of anaerobic metabolism, then I'll proceed directly to sedation and paralysis after explaining to the patient why I am inducing a short period of muscle relaxation for 6 hours, or about one half-life of 0.1 mg/kg of pancuronium in order to resuscitate and stabilize the cardiorespiratory abnormalities causing failure of oxygenation.

Pierson: And you'll do it just for 6 hours.

Wood: That time is often sufficient to optimize O_2 delivery in relation to consumption. And then anxiolytics are withheld because I want to be sure that the central nervous system is normal, and so 6 hours—or whatever time it takes to fix what the underlying oxygen delivery problem is.

Dantzker: Larry, I'm surprised to hear you're so conscious about oxygen transport and delivery. I listened to the tape yesterday of the discussion of Dr Phang's paper,[1] and I gathered from Dr Cerra's comment and from yours that you thought that most of those patients were really not in a flow-dependent state, given the fact that they're really not oxygen-dependent anyway. Why worry so much about dropping oxygen consumption or . . .

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Wood: The key thing there is when we made those comments. I hope it comes out in the summary of this conference that those are resuscitated patients. What we're talking about here is on the way to resuscitation. It is really easy to get oxygen supply-dependent anaerobic metabolism in a whole variety of clinical cases before you resuscitate the patient. What we're talking about is on the way to resuscitation; so, what we said yesterday (as I understood it) was once the patient's resuscitated, there is no flow-dependence of metabolism. That was my understanding of the conversation and the patients that Dr Phang presented that helped convince me. In the patients we're talking about here, in whom I think there's no pathologic supply-dependence, it's just that the exercise, the literal exercise of breathing, moving, working against the ventilator, and pyrexia have gotten the patient's requirement for a cardiac output in the face of this desaturation and anemia up to 18 L/min. In those circumstances, that patient needs help in terms of decreasing the oxygen demand, so that he doesn't need to have that much of a supply. That's what I was talking about.

Morris: Dr Cerra pointed out that oxygen might be an antibiotic. Years ago, many of our colleagues in infectious disease argued quite strenuously that pyrexia was an important element in the body's response to infection. Just a question, no suggestions. Couldn't the attack upon pyrexia (in which I participate and have participated) result in both a lowering of oxygen consumption and impairment of defenses against infection, and, therefore, have a rather problematic impact upon patient outcome?

Stoller: It's obviously a provocative idea that has been discussed in fever

circles for a long time. Although I think if I polled the audience again with regard to strategies, not of hypothermia but of euthermia, we might actually reach some more unanimity of approach. That is to say that cooling patients, with attention to paralysis (after the conventional strategies of antipyretics have failed), might be something that more of us would do. I think that that's certainly been our practice, as it sounds like it is yours.

Morris: Ten years ago, if you had asked me whether I was concerned about paralysis, I would have said no. Now, if you ask my colleagues and me whether we're concerned about paralysis, we'd say we're not so sure—having taken care of a number of patients who post-paralysis continue to be paralyzed. We're not quite clear as to why or how or in whom, and so forth and so on.

Stoller: I take the point.

Cerra: When do you think hyperthermia is a problem? We don't treat it until the temp consistently exceeds 103°F, as long as we can show that there's no problem in oxygenation or perfusion. Treating the lower fevers may result in a loss of the beneficial effect of hyperthermia on bacterial growth. For the same reason, we don't give iron to sick patients; the database for that is pretty scanty. On the other hand, I would ask, What is the normal temperature of an ICU patient? To me, most patients with an inflammatory response run around 101-102°. We've got plenty of fuel on the shelf. This is not a calorie problem, not even a work problem if we match the ventilator to the patient. It's very unusual for us to paralyze anybody. If you pay attention to matching the ventilator to the patient, instead of the patient to what your preconceived notion of what the ventilator ought to be doing, it's not a work problem. About the only situation in which we will use paralysis is when we're going to employ an alternate mode of ventilation, some form of inverse I-E ratio or pressure limited. Those patients almost always seem to need paralysis. There's another observation from the nutrition experience that I think needs to come in here about paralysis, paralysis can and does increase the rate of nitrogen loss from skeletal muscle. In the survivors that you get out of this hypermetabolic organ-dysfunction syndrome, the major problem is rehabilitation. Rehabilitation duration is directly correlated with how much lean body mass there is when its begun. I guess the last observation I would make about paralysis is about this whole issue of neuromuscular dysfunction in patients with multiple organ dysfunction. A polyneuropathy of persistent inflammation and organ failure has been described. It is both sensory and motor and also involves primary atrophy of skeletal muscles. It occurs independent of the presence of paralysis and may be part of the organ failure process itself.

Wood: I agree with everything that you just said. I don't think that we should paralyze any critically ill patient. But when a patient is on 0.60 or greater F_{IO_2}, and 15 cm or more of PEEP, and presents signs of anaerobic metabolism, I begin to look around for other things that I can do to either increase the supply or decrease the demand. That's when that sequence of getting the patient's work down comes into play. So, it's almost a salvage therapy to aid resuscitation at a critical time in a small number of patients. When such patients are paralyzed, they can benefit further by having their body temperature reduced to normal. I frequently find febrile patients on cooling blankets without paralysis. I try to get them off as quickly as possible because they're very uncomfortable, and the cooling has increased their metabolic demand, not decreased it, because of the metabolic cost of shivering. So, what's my favorite temperature? When I inherit the patient with oxygenation failure, he is often on a ventilator because of cardiopulmonary deterioration and on a cooling blanket to reduce body temperatures > 39° to normal to reduce $\dot{V}_{O_2}$. But there are few data about how much. What we're trying to do is get some of the data that you have asked for to find out what are the effects of lowering the temperature on $\dot{V}_{O_2}$, D_{O_2}, and O_2 extraction. Notice that these are all hemodynamic or gas exchange variables as the end points of manipulation of O_2 consumption—we need more. This is the first discussion in which Al Morris hasn't called for an outcome study, and we haven't even talked about it—not a word about whether reduction of $\dot{V}_{O_2}$ has any outcome effect, except for the long-term paralysis.

Nelson: Just a couple of points about paralysis. We never paralyze patients. If we do, it's salvaging them—things are out of control and you have to do something to calm the patient down. If you get the ventilator adjusted properly, the patient usually will be quite comfortable. Paralysis is what the housestaff like to do, their threshold seems to be the venous oxygen desatuation, which occurs well before arterial desaturation (even though you will see falls in S_{aO_2}, if the patients have shunt or a lot of low $\dot{V}/\dot{Q}$ areas). But I would venture to say that there's no difference in outcome between your unit where you paralyze a large fraction of patients, and our units where we never paralyze them. And I don't think we will ever see a difference. It's probably a moot point, except to match the ventilator with the patient's needs.

The second comment is about the patients with a very high oxygen consumption—200 mL/min. Again, from the database that we've collected, about 2,500 metabolic measurements of very sick patients, less than a half a per cent of all patients even approach that kind of metabolic rate. We're normally looking at the sickest patients in the ICU, and I would bet you those people are either very agitated or they're shivering or there's something else going on to get that kind of metabolic rate.

The last thing I'll throw open and would like to have some input on, you mentioned the term oxygen cost of breathing. That term always bothers me, because I don't know how to assess that. I know that in the patients that we've paralyzed, thinking that they have a terrible oxygen cost of breathing, how do we know how much of this is skeletal muscle when a patient is flailing around and agitated, and how much of it really is respiratory, and are there data on that? Does somebody know how to study that?

Stoller: Well, two points of correction. First, I think the issue of how many patients do you paralyze may be much like what Alan Morris was alluding to. We see the sickest patients in the unit's beds. Actually, we don't paralyze very many patients. It comes up in the same context of what you would regard as salvage therapy, so I have the kind of Wittgenstein approach to this—"Of that which you know little, say little." I mean, we don't do it because we don't really know its impact. With regard to how much is respiratory versus skeletal muscle literature, the literature I know the best in that regard is perhaps a little bit far afield of this, but it has to do with weaning patients, where cost of breathing measured pretty much in the way it's been alluded to, has been looked at as an independent weaning parameter.[1]

1. Shikora SA, Bistrian BR, Borlase BC, Blackburn GL, Stone MD, Benotti PN. Work of breathing: reliable predictor of weaning and extubation. Crit Care Med 1990;18:157-162.

Pierson: I would just like to agree with what Larry (Wood) said, no critically ill patient should ever be paralyzed unless there's absolutely no way around it, and my comment about the high frequency of paralysis use in our units, is not meant to indicate what Len (Hudson) and I would like to see done. We regard this as a major educational and behavior modification problem in our units.

Morris: I'd like to comment on your interesting choice of words. Several of us have used the term salvage therapy, with the implication that the therapy saves. That's what salvage means. I think that's an interesting prejudice, which we've introduced into the business. Everybody has admitted that we don't really know what the therapy does. So, I think salvage falls into the same category as improved P_{O_2} or improved x-ray. It carries a very important psychological imperative that tends to drive the action. If the residents tell me that the x-ray has improved or the x-ray has gotten worse, I usually tell them to run downstairs with the x-ray, get a big paper punch, punch a hole right over the tracheal column, and slip a tube in it. If it looks that bad do something right away. Then they look at me like I'm crazy, but I say x-rays can't improve or get worse; patients can, but not x-rays.

Hudson: But aren't most people using it when they think that therapy doesn't have any effect. I mean we're talking about it when it's desperate.

Morris: Yeah, but I think if the principle of beneficence is the real imperative, then Hippocrates was on the money when he said "First, do no harm." If Loeb was right when he said "If you don't know what you're doing, don't do anything," let's not take it to the logical conclusion, because I have a kid in college, and I can't afford to lose my job. But I think those things are imperatives. Then it seems to me that—regardless of whether we're treating a child with a strep throat who is not critically ill or whether we're treating the child's parent who has streptococcal sepsis, a devastating illness—the introduction of *any* therapy still has to be weighed in terms of whether the benefit accrued by the patient or delivered to the patient outweighs the harm. The term "salvage therapy" reminds me of the ECMO trial. We had this *de jure* death condition that permitted ECMO to be used as a *salvage* therapy, the implication being that it was improper to deny the patient the benefits of our therapy. I'm a little concerned about that. Louis XVI received the benefits of the best medical care in his time. He was purged 1,100 times. I don't perceive that as being a particularly helpful approach. Anyway, we could go on and on and talk about medical history. So, our choice of words is actually a very powerful determinant in many ways, and I would think about this.

Stoller: I agree with "last resort" as opposed to "salvage." I think most of us could agree that . . .

Morris: I think I would find that more comforting because "last resort therapy," then, at least raises in my mind this issue of major uncertainty, and might even help us in court.

Stoller: Although I suspect that in approaching your patients in desperate situations, probably the term "last resort" is used much more frequently

in patient conversations than the word "salvage." So . . .

Wood: I want to respond to that. I also think words are important, and, so, they also are efficient. We use them to get across an idea, and then, when the idea isn't understood accurately, we refine them. Whenever there's doubt about what a word means, then we talk about what it means. So, here's a 32-year-old patient with a P_{O_2} of 27, and a brand new pneumonia and temperature of 40°. It is not salvage therapy to intubate that patient and put him on a ventilator. OK? Now, on the ventilator on 100% oxygen, the P_{O_2} is 37, the saturation is 52%, and somebody thinks that maybe some positive end-expiratory pressure (PEEP) might help this patient. But they understand that because it's pneumonia, PEEP might not help. So they do it cautiously. That's not salvage therapy. All right? Saturation goes up. We haven't gotten to salvage therapy yet; we're not even 'last-resorting' anything. We're just escalating the level of therapy to some titrated end points, and the end points have no outcome value. PEEP has never had a prospective trial; PEEP has never had an outcome study. So all we're talking about is something as experimental as high frequency jet ventilation, except it's PEEP, and everybody here says, "I know PEEP fixes oxygenation, but it doesn't necessarily fix outcome." But, on the other hand, I don't think I'm going to withhold it in this patient, and I frequently don't. I choose to seek a physiologic end point with the least amount of intervention because PEEP can cause barotrauma—so, I seek the least level of PEEP that'll provide 90% saturation of an adequate circulating hemoglobin on a nontoxic F_{IO_2}. Now, each of the four components of this goal have some concerns about them and they lack outcome data, so I use physiologic improvement as a target for resuscitation until outcome data are available. Now, what am I going to do with this patient's $\dot{V}_{O_2}$ since his temperature is 39°, and he has pneumonia? If I lower the $\dot{V}_{O_2}$, am I at salvage yet? See, if I do sedate, paralyze, and cool the patient, the following things are going to happen. The measured $\dot{V}_{O_2}$ is going to go down, and the measured mixed venous O_2 saturation is going to go up, provided that I don't let my intervention interfere with the patient's cardiac output. Those are the mental constructs in which I'm now working. Am I to 'salvage' yet, or am I still following an established rationale for resuscitation? So, that's the term that Al (Morris) is asking for clarification, and I don't think that I'm at a last resort with this patient, but we're right on the topic that Stoller presented to us, which is whether there is any role for lowering the oxygen consumption? Clearly, we are pushing our new knowledge about $\dot{V}_{O_2}/D_{O_2}$ balance to provide a new rationale for resuscitation—when stated clearly, the rationale becomes a hypothesis to be tested.

Hess: Len, would you like to salvage this for us?

Hudson: No, I'd like to change the subject, but . . . I haven't reviewed the hypothermia papers for a long time, but it struck me that a lot of the animal model papers are short-term hypothermia, but that there were at least two papers (and maybe more)[1,2] that studied hypothermia of 24 hours or more, which are hard studies to do. They showed different results, in terms of hemodynamics, than the results from acute hypothermia and rewarming. That's one of the reasons that I agree with the principle that Alan (Morris) suggested, that we probably don't know enough about this because we're really looking at short-term studies. What we usually do is make patients hypothermic for longer periods of time. Do you recall any differences in those studies?

1. Steen PA, Milde JH, Michenfelder JD. The detrimental effects of prolonged hypothermia and rewarming in the dog. Anesthesiology 1980;52:224-230.
2. Morray JP, Pavlin EG. Oxygen delivery and consumption during hypothermia and rewarming in the dog. Anesthesiology 1990;72:510-516.

Stoller: I can't recall a total duration in those things off-hand, but I've used the work.

A Mechanistic Approach To Providing Adequate Oxygenation in Acute Hypoxemic Respiratory Failure

LDH Wood MD PhD and Jesse B Hall MD

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Introduction

Acute hypoxemic respiratory failure (AHRF) most commonly develops as a result of heart failure (cardiogenic pulmonary edema), acute lung injury (adult respiratory distress syndrome, ARDS), or pneumonia.[1] Despite these diverse etiologies, patients with AHRF experience a common life-threatening emergency—inadequate tissue oxygenation as a result of a large intrapulmonary shunt ($\dot{Q}_{sp}/\dot{Q}_t$), due in turn to flooding of air spaces by transudate, exudate, pus, or blood.[2] Accordingly, the initial objective of the critical care team is to establish an airway, initiate ventilation to prevent untoward respiratory muscle fatigue, and provide oxygenation, while simultaneously ensuring an adequate circulation. Because the goal of any one therapeutic intervention may confound another, optimal initial therapy is aided by a mechanistic understanding and explicit statement of the aims and adverse effects of each intervention.[3] In comparison to the therapeutic approach based on maximizing cardiac output (C.O.) and oxygen delivery (D_{O_2}) in septic shock,[4-6] such a mechanistic approach to AHRF can appear to conflict by pursuing a goal of adequate D_{O_2} in order to minimize lung edema. We contend that this apparent conflict is resolved when the immediately life-threatening disorder being treated is identified; patients with septic shock benefit from circulatory resuscitation without suffering the adverse effects of pulmonary edema, whereas patients with AHRF benefit from reduced lung edema without the adverse effects of shock.

This mechanistic approach begins with the assumption that air-space edema is the problem that necessitates ventilator therapy in patients with AHRF and that clearance of the air-space edema is essential for the liberation of the patient from the ventilator and from ICU management. Note that the mortality and morbidity in AHRF are due to the associated multiple systems organ failure (MSOF), to inadequate C.O. and D_{O_2}, and to complications of critical care.[7,8] Yet, the incidence and severity of

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these secondary causes of death and disability in AHRF are themselves proportional, at least in part, to the amount of alveolar flooding binding the patient to the ventilator and the ICU. In this paper, we review the interactions between respiration and circulation to provide therapeutic goals minimizing edema while maintaining adequate D_{O_2} and peripheral perfusion during the early management of the patient with AHRF; these goals are then modified for the patient whose acute exudative phase of lung injury proceeds to the proliferative phase of diffuse alveolar damage.[9,10]

Case Presentation

A 35-year-old male physician had been treated for neural deafness with 16 mg/day of dexamethasone. After 7 weeks of this therapy, he developed a dry cough, fever, and tachypnea. Results of physical examination, chest radiography, and arterial blood gas analysis led to his hospital admission for diagnosis and management of pneumonia in an immunocompromised host. The administration of intravenous fluid and antibiotic therapy was associated with rapidly progressing cyanosis, dyspnea, an increase in respiratory rate to 35/min, and arterial blood gas values of P_{aO_2} 50 torr, pH 7.22, and P_{aCO_2} 35 torr on a high-flow rebreathing mask. He was intubated and transferred to the University of Chicago. Initial management upon transfer included ventilation (tidal volume, V_T, 500 mL; ventilator frequency, f, 30/min; positive end-expiratory pressure, PEEP, 10 cm H_2O; fractional concentration of inspired oxygen, F_{IO_2}, 1.0), sedation with morphine, and paralysis with pancuronium. His blood pressure (BP) fell from 130/85 to 90/70 mm Hg, and his heart rate rose from 100 to 120 beats/min; although he was still febrile (39.5°C), his digits were cool, the nail-bed perfusion-return was slow, urine output decreased to 20 mL/h, and a significant metabolic acidemia was present. Because his jugular venous pulse was elevated and a gallop rhythm was heard, echocardiography was performed and revealed a normal-to-large heart with poor systolic function of both ventricles. A right heart catheter was inserted and revealed a pulmonary capillary wedge pressure (P_{pcw}) of 22 mm Hg and a C.O. of 3.9 L/min. The chest radiograph demonstrated four-quadrant airspace filling with right-lung air bronchograms compatible with pneumonia, cardiogenic pulmonary edema, or ARDS. The liquid suctioned from the endotracheal tube looked like plasma and had an albumin concentration of 3 g/dL when plasma albumin was 4 g/dL, confirming increased pulmonary capillary leak aggravated by high pulmonary vascular pressures due to iatrogenic fluid overload and global systolic left ventricular (LV) dysfunction, without electrocardiographic changes or elevated cardiac enzymes. Presumably, hypoxemia, acidemia, and ionized hypocalcemia were responsible.

Table 1 summarizes this patient's course in terms of the aerobic limits of metabolism. On transfer, the patient displayed a marked lactic acidemia, presumably due to his low C.O., anemia (Hb 10 g/dL), and hypoxemia (S_{aO_2} 65%). Initial resuscitation consisted of infusions of dopamine (3 $\mu g \cdot min^{-1} \cdot kg^{-1}$), dobutamine (6 $\mu g \cdot min^{-1} \cdot kg^{-1}$), and 3 units of packed red blood cells, with simultaneous vigorous diuresis induced by furosemide to reduce P_{pcw} while increasing D_{O_2}. C.O. increased to 5 L/min and hemoglobin to 15 g/dL; so, D_{O_2} doubled, mixed venous P_{O_2} ($P_{\bar{v}O_2}$) increased, and oxygen consumption ($\dot{V}_{O_2}$) increased immediately. Over the next 48 hours, the reduction in P_{pcw} was associated with improved pulmonary oxygen exchange, such that S_{aO_2} was greater than 90% when F_{IO_2} was 0.5 and PEEP was 5 cm H_2O; by that time, the lactic acidemia had resolved in response to this three-pronged increase in D_{O_2} (C.O., S_{aO_2}, Hb), aided in part by lowering $\dot{V}_{O_2}$ through mechanical ventilation and cooling of this hypermetabolic patient.

Table 1. Management of Oxygenation Failure in a Patient with AHRF and Septic Shock

	On Transfer	At 48 Hours	With Septic Shock	After 48 Hours
Temperature (°C)	39.5	37	40	37
Blood pressure (mm Hg)	95/70	110/70	90/40	100/55
Cardiac output (L/min)	3.9	5.0	8.5	11.5
Pulmonary capillary wedge pressure (mm Hg)	22	5	5	15
PEEP (cm H_2O)	18	5	5	10
F_{IO_2}	1.0	0.5	0.4	0.5
P_{aO_2} (torr)	38	65	70	65
Hemoglobin (g/dL)	10	15	15	15
D_{O_2} ($mL \cdot min^{-1} \cdot kg^{-1}$)	6.0	14	23	30
$\dot{V}_{O_2}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	3.0	3.6	4.0	3.6
$P_{\bar{v}O_2}$ (torr)	26	38	48	50
Lactate (mEq/L)	12	2	18	4

After this initial stabilization, the patient underwent open-lung biopsy, which demonstrated both cytomegalovirus and pneumocystis pneumonia. The initial broad-spectrum antibiotics were discontinued, and the patient was treated with trimethoprim and sulfamethoxazole (Bactrim) alone, which facilitated intravenous fluid restriction to keep P_{pcw} low. This exudative phase of ARDS was stabilized within 48 hours (Table 1) and improved further as edema cleared, but the acute lung injury progressed over 3 weeks to a proliferative phase characterized by increased pulmonary artery pressure, increased ventilation requirement, and increased pause pressure for the same low V_T. Alveolar albumin concentration had risen to 5 g/dL with no change in plasma albumin, suggesting that the pulmonary vascular leak had healed; so, fluid restriction and vasoactive drugs were discontinued. Then his temperature rose and his blood pressure dropped from 130/80 to 90/40 despite increased C.O. (Table 1). Septic shock was diagnosed. Broad spectrum antibiotics were effective in treating *E coli* bacteremia. Vigorous volume infusion and vasoactive drugs (dobutamine and dopamine doses as before) raised P_{pcw} from 5 to 15 mm Hg and C.O. from 8 to 12 L/min. During this fluid resuscitation, there was a deterioration in pulmonary oxygen exchange that required increased PEEP and F_{IO_2} to maintain $S_{aO_2} > 90\%$. Lactic acidemia recurred despite a high D_{O_2} and $P_{\bar{v}O_2}$ (Table 1).

The patient survived these different therapeutic approaches—lowering P_{pcw} to reduce edema and then raising P_{pcw} and C.O. to effect resuscitation from septic shock—and has resumed his practice of medicine. In the ensuing discussion, we present the data and rationale supporting these two different approaches to providing tissue oxygenation in these two different life-threatening conditions.

Reducing Pulmonary Vascular Pressure Reduces Edema without Reducing D_{O_2}

Pathophysiology of Lung Liquid Flux

The mechanisms responsible for lung liquid flux[11,12] are recapitulated in Figure 1.[13] Pulmonary microvascular pressure (P_{mv}) drives an ultrafiltrate of plasma from the alveolar vessels into the interstitium, where pressure is designated as P_{is}. This fluid movement is opposed by the oncotic pressure difference between the lung vessels (π_{mv}) and the interstitium (π_{is}), which constitutes a diffusion gradient for water (from high water concentration in the interstitium to low water concentration in the vessels). If the pulmonary vessels were impermeable to plasma proteins (reflection coefficient, σ, = 1) the entire oncotic pressure difference would resist edema flux; but when $\sigma = 0$, plasma proteins leak as readily as water molecules, and none of the diffusion gradient for water is effective. Cardiogenic edema occurs when the left-ventricular end-diastolic pressure (LVEDP) is increased by left-ventricular dysfunction or by fluid overload, leading to an increase in P_{mv}. This drives excess edema fluid through the endothelium of the pulmonary microvessels, which has a conductance K_f. When cardiogenic pulmonary edema causes AHRF, it is often treated by preload reduction (by treatment with furosemide, morphine, or nitroglycerin), which reduces LVEDP and P_{mv} from their very high values toward more normal values, without much reduction in the C.O.; if C.O. decreases to an unacceptable level, positive inotropic agents like dobutamine enhance myocardial contractility to maintain stroke volume despite reduced preload, and vasodilating agents (eg, nitroprusside) allow the heart to eject to a smaller end-systolic volume, thereby maintaining C.O. at a lower preload.[1,11]

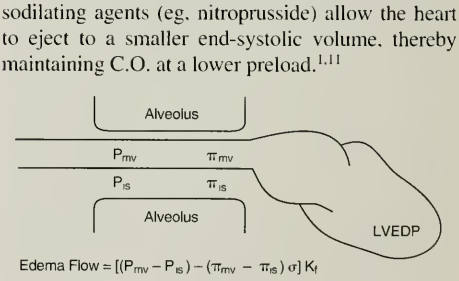

Fig. 1. The pathophysiology of increased edema flow in acute hypoxic respiratory failure (see text for details and definitions). (Reproduced from Reference 13, with permission.)

Following acute lung injury in ARDS, K_f increases markedly, and the σ decreases so that alveoli flood with a protein-rich exudate despite normal or even reduced values of P_{mv} and LVEDP. Most patients with ARDS or pneumonia maintain normal or increased C.O. despite normal values of P_{mv}, in part due to the stimulation of the circulation from tissue hypoxemia, endogenous catecholamines, the increased metabolism of concomitant sepsis, and the

work of breathing. This exudative phase of diffuse alveolar damage is associated with a high protein content in the bronchoalveolar lavage liquid. As the acute lung injury begins to heal, active sodium and water transport clear the alveolar edema but concentrate the alveolar protein so that the alveolar protein concentration rises above that in the plasma; this marker of healing is associated with an increased survivorship as well as a decrease in the lung liquid flux.[14] Other noninvasive studies of pulmonary vascular permeability are becoming available to guide cardiovascular management of lung leak (eg, the study by Kaplan et al[15]); these studies demonstrate a large protein permeability in pneumonia as well as in ARDS, accounting for the marked worsening of AHRF after fluid resuscitation.[16]

In a canine model of acute lung injury induced by oleic acid, reduction of the P_{pcw} by 5 mm Hg was associated with a 50% reduction in pulmonary edema during a 4-hour treatment period; by contrast, increasing π_{mv} while maintaining P_{pcw} constant had no effect on edema accumulation, as would be expected when σ was very low, and K_f was very high.[17] That study indicated that when the P_{pcw} was reduced with vasoactive drug therapy (sodium nitroprusside), the C.O. and D_{O_2} were not reduced. Figure 2 summarizes the time course of edema, shunt, and C.O. in six other studies of canine lung injury induced by either hydrochloric acid aspiration[18-21] or kerosene aspiration[22,23] when treated by reduction of pulmonary vascular pressures. In each of these studies except control (P_{pcw} = 12 mm Hg) and indomethacin administration, P_{pcw} was reduced by 4-7 mm Hg—beginning 1 hour after the aspiration lung injury. As indicated in Panel A, pulmonary edema increased linearly with time in the control group and with indomethacin but stopped increasing when the P_{pcw} was reduced by plasmapheresis (Pl) or by nitroprusside infusion (NP); by 5 hours, this treatment reduced extravascular lung liquid (EVLL) by more than 50%, a result confirmed by gravimetric analysis of edema in the excised lungs.[17-23]

The corresponding changes in C.O. are indicated in Panel C of Figure 2. Plasmapheresis to reduce P_{pcw} to 8 or 5 mm Hg reduced the C.O. compared to the control group with a constant C.O.; yet, when Pl reduced P_{pcw} to 5, C.O. was maintained as in the control group by infusion of dopamine (Dop) or nitroprusside. In fact, D_{O_2} was actually increased in the plasmapheresis and dopamine group because Pl increased the hematocrit.[18,19] Note that hemofiltration reduced P_{pcw} but did not reduce edema. Note further that indomethacin reduced C.O. at the same P_{pcw} (12 mm Hg); this adverse cardiovascular effect did not reduce edema but did reduce shunt.[21] Panel B shows the corresponding change in shunt ($\dot{Q}_{VA}/\dot{Q}_t$, measured on F_{IO_2} 0.6). In the control group, $\dot{Q}_{VA}/\dot{Q}_t$ rises in a non-linear manner with EVLL. By contrast, when the P_{pcw} and edema were reduced, $\dot{Q}_{VA}/\dot{Q}_t$ also decreased. Comparison of Pl with Pl + Dop indicates that for the same amount of edema (Panel A), the increase in C.O. with dopamine is associated with an increase in $\dot{Q}_{VA}/\dot{Q}_t$. These data agree with clinical[24] and animal experiments[25] that suggest a positive correlation between shunt and pulmonary blood flow; this relationship has but a small effect

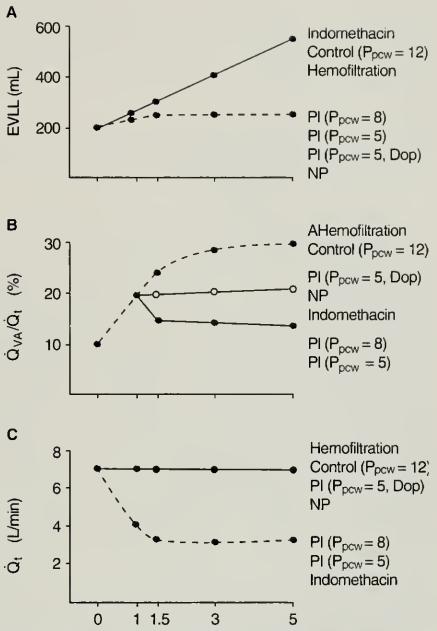

Fig. 2. The effects of reducing pulmonary capillary wedge pressure (P_{pcw}) after hydrochloric acid or kerosene aspiration at time 0 hours (abscissa) on extravascular lung liquid (EVLL), shunt ($\dot{Q}_{VA}/\dot{Q}_t$), and cardiac output ($\dot{Q}_t$); see text for details. Data from six canine studies (based on data from References 18-23). (Reproduced from Reference 1, with permission.)

on D_{O_2} because arterial oxygen content (C_{aO_2}) falls only a small amount, if at all, when shunt and mixed venous oxygen content ($C_{\bar{v}O_2}$) increase with C.O.[17-20,24]

Pitfalls in Pursuing the Least Circulating Volume Providing Adequate D_{O_2}

These animal studies[17-23] confirm that lung edema in the exudative phase of acute lung injury can be markedly diminished by reducing the P_{pcw} without reducing the C.O. When this approach was tested in patients with ARDS, mortality in the group in whom P_{pcw} was reduced by 5 mm Hg or more was only 25%, contrasted with a mortality of 71% in the group in whom P_{pcw} was not reduced (Table 2). The duration of both ventilator therapy and ICU care was reduced in the 5-mm Hg group.[26] Other clinical studies demonstrate that negative fluid balance[27,28] or EVLL reduction[29,30] improves survivorship in patients with AHRF. An essential component of this approach is to ensure that the C.O. is adequate when P_{pcw} is reduced.[1,3] An adequate C.O. is best indicated by clinical examination—adequate pulse pressure and mean perfusion pressures, warm digits with good nail-bed perfusion-return, and absence of tachycardia, prerenal oliguria, and lactic acidosis.[12,31] What is accepted as an adequate perfusion pressure varies in that an elderly patient with significant vascular occlusive disease needs a higher blood pressure than a young patient with no evidence of vascular disease.

Table 2. Effect of Reducing Pulmonary Capillary Wedge Pressure (P_{pcw}) in ARDS*

	Group 1	Group 2
P_{pcw}† on entry	13.0 (4.0)	11.4 (2.0)
P_{pcw} at 24 hours	6.5 (4.5)‡	13.0 (5.0)
P_{pcw} at 48 hours	7.7 (1.5)‡	13.0 (6.1)
Number of patients	16	24
Number of survivors	12	7
% survived	75	29§

*Assembled from data published in Reference 26.
†All P_{pcw} values are mean (SD) mm Hg.
‡Denotes significant difference from entry values ($p < 0.01$).
§Denotes significant difference from Group 1 survival ($p < 0.02$) by χ^2 Maentel Haenzel.

This clinical evaluation of adequacy of the circulation may be aided by measurements of thermodilution C.O., pulmonary vascular pressures, and the arterial-to-venous content difference ($C_{aO_2} - C_{\bar{v}O_2}$). It is important to notice that the lowest P_{pcw} that provides an adequate peripheral perfusion varies from < 0 mm Hg to > 20 mm Hg, depending on the degree of ventricular dysfunction.[32] Furthermore, the measured value of C.O. consistent with adequate peripheral perfusion varies with the patient's size and metabolic activity. Accordingly, there is no predetermined target value for either P_{pcw} or C.O.; instead, the goal for a given patient is the lowest value of P_{pcw} consistent with a measured C.O. that excludes clinical hypoperfusion. It follows that this approach does not require heart catheterization because the same goals are achieved by seeking the lowest circulating volume compatible with adequate peripheral perfusion. With this conceptual approach, the measured values of P_{pcw}, C.O., and $C_{\bar{v}O_2}$ may provide some additional information as to what values indicate adequate perfusion; then these data from right heart catheterization are used to titrate toward the least values providing adequate perfusion and to guide immediate plasma volume expansion and vasoactive drug therapy when a state of hypoperfusion is detected early.[1,3,31,32] In this way, right heart catheterization is limited in AHRF to those patients in whom these hemodynamic questions cannot be answered by clinical examination. Even experienced intensivists err in their clinical assessment of pulmonary vascular pressures and adequacy of C.O.;[33,34] so, a low threshold for obtaining this hemodynamic information seems appropriate in very ill patients. Of course, beneficial use of the data is dependent upon correct interpretation and timely titration toward a clear hemodynamic goal—the least P_{pcw} providing adequate C.O. By its definition, this approach cannot cause shock or organ ischemia, but it does manage the patient with AHRF closer to the lower limit of adequate perfusion; therefore, the physician needs to be attentive to early signs of hypoperfusion in order to correct it immediately.

When one targets the least circulating volume to provide adequate D_{O_2}, four clinical problems may be encountered. First, left ventricular dynamic outflow obstruction occasionally occurs in relatively hypovolemic patients treated with dobutamine—especially elderly hypertensive patients; sudden hypo-

tension in such patients warrants echocardiography for diagnosis, discontinuation of dobutamine, and plasma volume expansion.[32] Second, some patients with AHRF, especially with concurrent sepsis, develop systemic vascular leak and can accumulate 15 to 20 kg of excess liquid while the lowest P_{pcw} that ensures an adequate C.O. is maintained; because this excess liquid is shared by the lungs and may confound the function of other organs, we encourage early hemofiltration or vigorous diuresis aided by albumin or plasma infusion just as soon as the vascular leak is corrected.[1,11] Third, positive pressure ventilation and PEEP cause a problem for intensivists who ask, How much is the pressure outside the heart increased? We contend that the answer is best obtained functionally by seeking the lowest P_{pcw} for each required PEEP level and V_T that provide an adequate C.O. Then we continuously seek the least PEEP and V_T to achieve the goals of these ventilation therapies as discussed below.

Fourth, there is a special problem in septic patients with AHRF in understanding what constitutes adequate C.O. and D_{O_2}.[35-37] Because sepsis syndrome and ARDS often occur in the same patient, priority must be given to ensuring an adequate C.O. and D_{O_2} even when the higher circulating volume increases the edema. Yet, the end point of maximizing D_{O_2} is not clear because we have no sensitive and specific indicators of the anaerobic metabolism that high D_{O_2} is assumed to treat.

Rational Maintenance of D_{O_2} at Reduced Pulmonary Vascular Pressures

Throughout this conference, one suggested index of hypoxia has been the reduction in $\dot{V}_{O_2}$ in conditions of decreasing D_{O_2}. Figure 3 indicates that this supply-dependence of $\dot{V}_{O_2}$ occurs in patients with normal metabolism ($\dot{V}_{O_2}$ = 3-5 mL · min^{-1} · kg^{-1}) when D_{O_2} is abnormally reduced into the range of 5-7 mL · min^{-1} · kg^{-1}.[35] Then the extraction fraction (EF, right ordinate) cannot increase beyond a critical value (EFc = 0.67), so $\dot{V}_{O_2}$ is diminished associated with lactate acidosis. In AHRF, $\dot{V}_{O_2}$ is much increased by some combination of fever, sepsis, work of breathing, trauma, burns, or surgery.[36-38] In the circumstance indicated in Figure 3, the $\dot{V}_{O_2}$ has tripled to 12 mL · min^{-1} · kg^{-1}, when even a normal ability of the tissue to extract oxygen necessitates a D_{O_2} of 18 mL · min^{-1} · kg^{-1} to maintain aerobic metabolism. Because that high value necessitates a high C.O., in turn requiring a high P_{pcw}, one approach to maintaining aerobic metabolism is to reduce $\dot{V}_{O_2}$.[2,35] Accordingly, the early resuscitation of the patient with AHRF might include intubation and ventilation to decrease the work of breathing. Often hypoxic patients continue to breathe spontaneously despite being placed on the ventilator; sedation and muscle relaxation for a short period ensure a reduction in this unnecessary exercise.[1,39] Once muscle relaxation has occurred, fever may be reduced with antipyretics and a cooling blanket[2,40] while early antibiotic therapy and surgical removal of sources of sepsis all reduce that part of the increased $\dot{V}_{O_2}$ due to hypermetabolism.[36,37] As the $\dot{V}_{O_2}$ is being reduced, D_{O_2} can be increased by raising the circulating hemoglobin concentration to 15 g/dL and by raising S_{aO_2} by increasing F_{IO_2} and PEEP (provided that the latter does not reduce C.O.);[2] in extreme hypoxemia, hyperventilation to respiratory alkalemia may improve arterial saturation without confounding tissue oxygen extraction.[41]

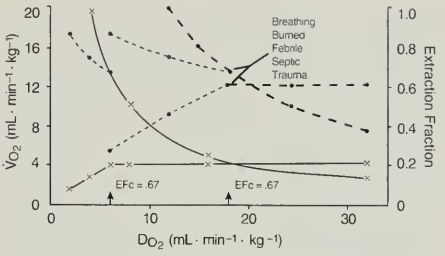

Fig. 3. Oxygen consumption ($\dot{V}_{O_2}$, left ordinate) and O_2 extraction fraction (EF, right ordinate) are plotted against O_2 supply (D_{O_2}, abscissa) for a hypothetical afebrile ventilated patient ($\dot{V}_{O_2}$ = 4 mL · min^{-1} · kg^{-1}, continuous lines through x) and for the same hypothetical patient with AHRF who is breathing spontaneously and is hypermetabolic due to burns, trauma, fever, and sepsis ($\dot{V}_{O_2}$ = 12 mL · min^{-1} · kg^{-1}, interrupted lines through closed circles). Even if the tissue ability to extract oxygen is normal (EFc = 0.67), the hypermetabolic patient needs a D_{O_2} of 18 mL · min^{-1} · kg^{-1} to maintain aerobic metabolism. See text for details. (Reproduced, with permission, from Reference 38.)

A sample calculation may be revealing. In a patient weighing 100 kg, it can be shown by the inter-

rupted line in Figure 3, that the C.O. required to maintain aerobic metabolism is 18 L/min when the hemoglobin concentration is 9 g/dL and the S_{aO_2} is 80%. Raising the hemoglobin to 15 g/dL and the saturation to 90% reduces the C.O. required to maintain $\dot{V}_{O_2}$ to 10 L/min. When $\dot{V}_{O_2}$ is reduced to 6 $mL \cdot min^{-1} \cdot kg^{-1}$ by removing the work of breathing and by decreasing the patient's core temperature to normal, the required C.O. falls to 5 L/min without any change in the oxygen extracting ability of the tissues. Of course, the value of P_{pcw} required to maintain the original C.O. of 18 L/min can be much reduced to maintain a C.O. of 5 L/min, so the pulmonary edema formation is much reduced.

During the last decade, this approach to seeking the lowest P_{pcw} compatible with adequate D_{O_2} has been confounded by the potential pathologic supply-dependence of oxygen utilization, by which tissues have a problem extracting oxygen.[35] Although the existence of pathologic supply-dependence of oxygen utilization has been clearly demonstrated in animal experiments,[35] its existence in patients with AHRF has not been confirmed by recent studies measuring $\dot{V}_{O_2}$ by methods independent from D_{O_2},[42-44] thereby avoiding a spurious correlation between $\dot{V}_{O_2}$ and D_{O_2}. A second conundrum resurfacing in septic patients, many of whom have AHRF, is that the lactic acidosis of sepsis is often not anaerobic.[36,45-47] To the extent that this is true, maximizing the D_{O_2} will not correct the lactic acidosis. Therefore, lactic acidemia in the septic patient should invite the physician to evaluate the adequacy of perfusion rather than to trigger a maximizing of D_{O_2}. In such septic patients, it seems reasonable to effect a vigorous fluid and vasoactive resuscitation of their hypoperfused state to include a supranormal C.O.;[6] further increases in D_{O_2} do not improve tissue oxygenation.[6,44] If subsequent studies establish a beneficial effect of even higher C.O., the effect is likely to derive from tissue washout or transport of nutrients other than oxygen to ameliorate the inflammatory hypermetabolism.[47] It should be noted that the only controlled study of maximizing D_{O_2} in sepsis was terminated early because the investigating physicians were convinced of the value of this approach; yet, there was no significant difference in survivorship between the intervention and control group.[6]

On the other hand, maximizing D_{O_2} in the patient with AHRF who is not septic is often associated with increased circulating volume and P_{pcw}, both of which increase pulmonary edema, necessitating increased PEEP and F_{IO_2}. These interventions increase the risk of barotrauma and oxygen toxicity of the lung and prolong the duration of ventilation and the ICU stay, with their attendant complications. Implications of this mechanistic approach in AHRF without sepsis include restoring normal D_{O_2} and decreasing tissue oxygen demands; maximizing D_{O_2} on the remote possibility that there is an oxygen extraction defect seems to run a high risk of doing harm without conferring benefit.

Ventilator Management of AHRF

Because alveolar flooding causes intrapulmonary shunt refractory to even the highest F_{IO_2}, effective oxygen therapy requires several adjuncts.[2] The most effective is positive end-expiratory pressure (PEEP). When PEEP was applied to one lung in canine oleic-acid edema (Table 3), PEEP reduced shunt by redistributing alveolar edema from the air spaces into the pulmonary interstitium without reducing the pulmonary edema.[48] This recruitment of air spaces is associated with a much larger increase in end-expired lung volume than would be predicted from the respiratory compliance (C_R) and the addition of PEEP.[49,50] Figure 4 illustrates these respiratory mechanics in a canine model of acute lung injury.[51] The open circles and continuous lines indicate the inflation and deflation transpulmonary pressure-volume relationship in an injured lung venti-

Table 3. Effects of Unilateral PEEP on Lobar Shunt and Liquid Distribution in Canine Oleic-Acid Pulmonary Edema*

	No PEEP	PEEP
Lobar Shunt—%	48.1 (32.0)	5.9 (4.2)†
Extravascular lung liquid (EVLL)—mL/g‡	7.4 (2.4)	7.5 (2.6)
Cuff liquid—mL/g	2.4 (1.7)	3.8 (2.8)†
Alveolar liquid—mL/g	1.4 (2.2)	0.3 (0.7)†
% alveoli flooded	79.9 (13.5)	20.1 (16.0)†

*Adapted from Reference 48, with permission. Values are mean (SD) of 8 experiments.
†Denotes significant difference from the no-PEEP lobe ($p < 0.05$, paired t test).
‡Normal EVLL in uninjured canine lungs is 3.7 (0.2) mL/g dry weight.

lated with a large V_T and a low level of PEEP; note the very low inflation compliance of the lung (C_L) and the large pressure-volume hysteresis. When the PEEP is increased by 10 cm H_2O and the V_T is reduced by 50%, the lung deflates from its end-expired lung volume (indicated by Number 1) along the interrupted line to the end-expired lung volume after the first breath lying within the pressure-volume hysteresis. The second breath inflates the lung further, but again less V_T is expired than was inspired, so the end-expired lung volume increases to Number 2, now approaching the expired pressure-volume curve. By the fourth breath, both end-inspired and end-expired lung volumes have increased further. By 6-to-10 breaths, the new stable end-expired lung volume is indicated by the closed circle, and the pressure-volume hysteresis for the smaller V_T and higher PEEP is indicated by the inspired and expired transpulmonary relationship connecting the closed circles.

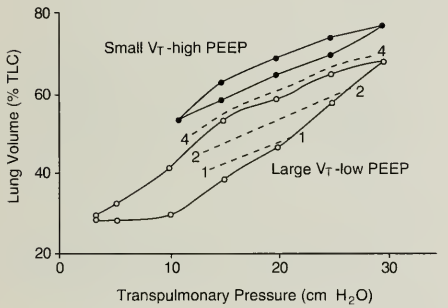

Fig. 4. Comparison of pulmonary pressure-volume relationships during canine acid aspiration pneumonitis between 2 groups: Open circles denote large-tidal volume (V_T) low PEEP (3 cm H_2O); closed circles denote small V_T-high PEEP (13 cm H_2O). The interrupted lines illustrate how a patient with a large V_T-low PEEP ventilatory pattern moves through the pulmonary P-V hysteresis with each breath after the V_T is reduced and PEEP is increased. See text for details. (Reproduced and adapted from Reference 51, with permission.)

Note that the increase in lung volume with PEEP is much greater than would be predicted from the low C_L because air spaces have been recruited by PEEP, thereby decreasing the intrapulmonary shunt. Because the end-expired lung volume is so large, it is helpful to reduce the V_T in order to minimize barotrauma. Indeed, the large V_T-low PEEP strategy increased the pulmonary edema considerably as compared to the high PEEP-small V_T ventilation strategy—perhaps due to aggravating the surfactant depletion of acute lung injury.[51,52] In these circumstances the V_T should be reduced to the smallest value that still provides adequate alveolar ventilation as indicated by absence of an unacceptable respiratory acidosis in the patient. Similarly the PEEP can be reduced to the lowest value that achieves the oxygenation goals—90% saturation of an adequate level of circulating hemoglobin (15 g/dL) on a nontoxic F_{IO_2} (< 0.6).

These least values of PEEP and V_T are sought to limit the barotrauma and hypoperfusion. The reductions in C.O. effected by PEEP are due to the increase in pressure outside the atrium.[49,53-55] and may be countered by interventions that increase the circulating volume and ventricular contractility.[1,12] Note that hypovolemic patients or those receiving medication that blocks venous tone (eg, morphine, furosemide, nitroglycerin) have much less ability to compensate for increased intrathoracic pressure with PEEP, so less PEEP can be employed until the circulating volume is increased.[1,12] Accordingly, the least PEEP should be used that achieves the goals of oxygenation, and positive inotropic agents or vasodilator drugs are used to decrease end-systolic volume to maintain stroke volume at reduced LVEDP.[12,32] Because critical illness imposes diverse etiologies of systolic and diastolic dysfunction (Table 4), it is helpful to exclude or treat each of these as part of an approach to minimizing P_{pcw} while maintaining D_{O_2}. Note that this obviates the need to know how much the pressure outside the heart increases with PEEP or other ventilator changes because the approach continually seeks the least P_{pcw} or circulating volume on each required level of PEEP and V_T; in turn, the lowest PEEP and V_T are concurrently sought to minimize barotrauma.

Consider the following application of these principles integrating ventilator and circulation management for the patient presenting with AHRF described at the beginning of this paper. After ascertaining the need for intubation and ventilation, we explain briefly to the patient that his illness requires short-term rest (< 24 h) on the ventilator during which he will be sedated and will not be able to move. The patient is then sedated, intubated, pro-

Table 4. Common Causes of Diastolic Dysfunction in Critically Ill Patients Signalled by High Left-Atrial Pressure and Low Left-Ventricular End-Diastolic Volume*

External Compression
Pericardial effusion or constriction
Positive pressure ventilation with PEEP
Tension pneumothorax, massive pleural effusions
Greatly increased abdominal pressure
Myocardial Stiffness
LV hypertrophy—aortic stenosis, systemic hypertension
Infiltrative diseases—amyloidosis
Ischemic heart disease
Ventricular Interdependence and Right-to-Left Septal Shift
Pulmonary hypertension
RV infarction
High levels of PEEP
Intraventricular Filling Defects
Tumor
Clot
Rhythm or Valvular Impediments to Filling
Tachycardia
Heart block
Atrial fibrillation, flutter
Mitral stenosis

*Reproduced from Reference 12, with permission.

vided muscle relaxation, and ventilated with 100% oxygen at V_T = 6 mL/kg and f = 30. While following the pulse oximeter readout (S_{pO_2}), we progressively increase PEEP from 0 to 20 cm H_2O over 5 minutes unless the BP falls to an unacceptable level. If the latter occurs, PEEP is reduced until the BP reduction is reversed, and an intravenous infusion of vasoactive drugs (dopamine 3 μg/kg; dobutamine 2 to 10 μg/kg) is initiated. Most often, this stabilizes the blood pressure at a value of PEEP providing ≥ 90% S_{pO_2}; if not, an urgent reevaluation with correction of intercurrent hypovolemia and anemia is initiated. Then the F_{IO_2} is reduced to 0.8; if S_{pO_2} decreases below 90%, PEEP is increased until S_{pO_2} exceeds 90% or BP falls unacceptably. Then F_{IO_2} is reduced to 0.7 and then 0.6 with the same precautions. Now the circulating volume is further reduced with morphine and a loop diuretic; packed red blood cells are infused to bring the hematocrit to 40%. Thereafter, this least circulating volume providing adequate C.O. is constantly sought while PEEP is continuously reduced toward the lowest value providing an S_{pO_2} of 90% with an adequate hematocrit (40%) on a nontoxic F_{IO_2} (< 0.6). This initial process requires less than 1 hour; it may be subsequently complemented by right heart catheterization (to provide the numerical values of C.O., P_{pcw}, and $C_{\bar{v}O_2}$ associated with these therapeutic goals; then these values are used as needed during the next 12-96 hours to liberate the patient from PEEP, elevated F_{IO_2}, vasoactive drugs, and the ventilator. This mechanistic approach is continued beyond 96 hours if there is evidence of continued pulmonary capillary leak;[14] if the abnormal permeability is corrected, fluid intake is liberalized and the P_{pcw} and circulating volume are allowed to increase to maintain C.O. and D_{O_2} without vasoactive drugs.

Summary

These therapeutic goals of the early management of AHRF in the absence of septic shock can be summarized.

- Seek the least circulating volume and pulmonary capillary wedge pressure compatible with an adequate oxygen delivery as indicated by an adequate blood pressure, pulse pressure, warm digits with good nail-bed perfusion-return, and absence of prerenal oliguria and lactic acidosis.

- Seek the lowest positive end-expiratory pressure providing 90% saturation of an adequate circulating hemoglobin on a nontoxic F_{IO_2}.

- Seek the smallest tidal volume providing adequate alveolar ventilation as indicated by an acceptable degree of respiratory acidosis.

We acknowledge that our attempt to influence the treatment of AHRF by these goals is not infrequently confronted by utter disbelief in some intensivist colleagues who are quite convinced that an opposite approach that maximizes D_{O_2} confers improved outcome.[4-6] We invite attention to the data upon which such protocols are based. These patients are not being treated for acute lung injury as an entrance condition, although some certainly develop pulmonary edema in the course of having D_{O_2} maximized. Rather, this patient population is largely skewed by high cardiac output hypotension and hy-

permetabolism, which may benefit from supranormal cardiac output.[6] When patients with septic shock develop a pulmonary vascular leak, it seems reasonable to question the evidence for inadequate perfusion before maximizing the circulating volume and pulmonary edema. In the absence of septic shock, patients with acute hypoxic respiratory failure experience adequate tissue oxygenation as their edemagenesis is reduced and their survival is enhanced by the application of this mechanistic approach.[26-30] When the exudative phase of AHRF abates,[14] the aggressive pursuit of the lowest circulating volume becomes less beneficial in the continuing management of the patient.

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Wood Discussion

Dantzker: Well, Larry, I probably could spend as much time asking questions about your report as you did doing it. I have just one simple question. How do you know it works?

Wood: What a good question. If anybody thinks that it might work—based on the animal experiments I just reviewed where it works in terms of diminishing edema, diminishing shunt, and increasing D_{O_2}, but with no survivor data—if anybody is convinced that it might work based on the 4 clinical studies showing increased survival with decreased circulating volume and lung edema—then we might need a controlled double-blind, randomized study that focuses on an approach that prospectively lowers the wedge pressure while maintaining an adequate D_{O_2} in one group of patients with AHRF, versus prospective maximizing D_{O_2} in a second group. My review of these papers already supports the former approach in early AHRF.

Dantzker: Well, let me just ask you one question. Do you believe that any of the organ failure that we see in patients like this has anything to do with oxygenation of the tissues?

Wood: Sure.

Dantzker: Because I see a different patient than you do, my patients don't have extraction ratios of 60%. They have extraction ratios of 30%. They don't have $\dot{V}_{O_2}$s of 12, they have $\dot{V}_{O_2}$s of around 4, and, yet, their organs suddenly stop functioning during that period of time. Dr Phang told us that he doesn't think there's any supply-dependence in those patients, and some data I'll show you tomorrow on what other people have found in terms of that status. I don't know how you determine what an adequate flow is. I'm not sure how you determine what an adequate hematocrit is—because certainly the peripheral hematocrit may not have anything to do with what the hematocrit is in the tissues.[1,2] So I'm still confused. I mean, I've heard all of these . . . this is what you all say when we wave our hands, but I'm not sure I understand the basis for this sort of approach to the patient.

1. Lipowsky HH, Firrell JC. Microvascular hemodynamics during systemic hemodilution and hemoconcentration. Am J Physiol 1986;250(6, Part 2):H908-H922.
2. Desjardins C, Duling BR. Microvessel hematocrit: measurement and implications for capillary oxygen transport. Am J Physiol 1987;252(3, Part 2):H494-H503.

Wood: David, you probably do understand the basis for the whole approach to the patient. In the first line of my presentation as I described my patient's chest radiograph, I reasoned that a patient with that amount of lung edema is going to be bound to the ventilator and the ICU until the edema that put him there goes away. That isn't the same as saying that the patient dies because of pulmonary edema. The mortality in ARDS is due to multisystem organ failure—various organs falling out. Intercurrent complications are the major causes. On the other hand, it has some rational basis that the longer that patients stay on ventilators in an intensive care unit, the more prone they are to complications. The answer to the question that you asked—"How do you know it works?"—would have to be a study like the one that I showed you[1-3] but done in a prospective, randomized fashion. The answer to the bedside question, "Is there more organ system failure that develops in the course of managing patients with early AHRF by maximizing the D_{O_2} or by seeking the lowest circulating volume providing an adequate cardiac output and D_{O_2}?" is not known. Organs do fail with either approach, but they shouldn't. In other words, we should be on top of the adequacy of the cardiac output and oxygen delivery so as not to let them fail, but that expectation needs to be tested.

1. Long R, Breen PH, Mayers I, Wood LDH. Treatment of canine aspiration pneumonitis: fluid volume reduction vs fluid volume expansion. J Appl Physiol 1988;65:1736-1744.
2. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. Chest 1990;97:1176-1180.
3. Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 1992;145:990-998.

Dantzker: The problem is, I think, that organs fail very rapidly. We don't really get a warning. One day you come in and the creatinine is starting to climb or the bilirubin is beginning to go up, and there has been no warning that that's happening. It's not like you can follow a number that says something is going wrong with those organs. All of a sudden they begin to fail. I'm not aware that there's any way of knowing that things are going to take place.

Wood: All I can say to that is I do see a different set of patients. I see progressive oliguria with specific gravity rising as prerenal oliguria sets in. Urine sodium drops to 20 and urine potassium jumps to 50, and unless somebody increases the renal perfusion before you come in in the morning, you're going to have an acute tubular necrosis on your hands. Now, you and I are almost certainly talking about the same scenario. I'm just upping the ante in terms of the vigilance with which one prevents inadequate D_{O_2}.

Nelson: When you started your talk, my first thought was that in 12 years of doing this sort of thing full time, I've never seen a patient at all like what you were talking about. And then you showed your summary slides of your treatment recommendations, and I thought, Yeah, I agree with all those things, and I think that's the right approach. A couple of thoughts came to mind. Denis Edwards uses two lines that I think are good for all of us to remember when he gives his talk about optimizing oxygen delivery. He uses one term, "Keep 'em dry, watch 'em die." I think that's pretty appropriate. And the second one is "The best way to prevent shock lung is to not treat shock." I think that's pretty appropriate, too. The problem that I see with all of the human studies and many of the animal studies that you showed is that they've not really looked at transmural filling pressures, either transpulmonary pressures or transcardiac pressures, to assess wedge pressure. About 2 years ago, Michael Banner introduced us to the Bicore pulmonary function monitor, and we've started using this in virtually every patient we treat with increased levels of end-expiratory pressure. It has turned our fluid management around 180 degrees. Now patients who have a wedge pressure of 30 are being treated with fluid boluses because their transmural filling pressures are zero when they're on 30 of PEEP. What do you think about that? I'd like to hear the comments. Are other people using this, or is it crazy to start looking at transmural things when most of the data available are looking at absolute pressures?

Wood: I think that if you think that your patient is hypovolemic, you should give a volume challenge. I don't need transmural pressure to have a suspicion that the patient is hypovolemic.

Nelson: What about the patient? Last week I had a patient to whom in 3 days I gave 140 liters of crystalloid. With the 139th liter he was still hypovolemic. His transmural went to zero, his urine output within an hour would fall to 5 mL/hour. His cardiac output would drop to a cardiac index of 1.5, and with a liter bolus of fluid would go back up to 3. His urine output would go to 60 mL/hour. His blood pressure would come back to 110.

Wood: Sounds like he's third-spacing.

Nelson: A little bit!

Wood: That's what I think about that. If he's third-spacing and I can't keep it in his vasculature until the peripheral leak stops, I guess I'd better keep giving enough circulating volume to keep his cardiac output adequate. I still don't need a transmural pressure to get it. You may be carrying coals to Newcastle, here. I'm familiar with transmural pressures—for example, all the canine data that I just reviewed measured transmural wedge pressures to evaluate and reduce the circulating volume to test whether this reduces edema. But when the clinical question is whether the cardiac output is adequate, the answer is in the clinical assessment of perfusion and the lowest wedge pressure is what achieves that cardiac output. The measured wedge pressure may be very high when echocardiography reveals a small left ventricle. I don't want to encourage people to have to think too hard about the mechanisms for transmural pressure, nor do I think it's very helpful to measure it because what you're looking for is what's the lowest wedge pressure that maintains an adequate cardiac output.

"Keep 'em dry, watch 'em die" is one of those platitudes that people get a lot of mileage out of; and when I hear it, I like to invite the people to come to the bedside and not watch 'em die, but make sure that the name of the game is watch 'em be adequately perfused. It is a reproducible phenomenon in the intensive care units where I work and where I visit that I can take whatever the wedge pressure is at a point in time and lower it considerably without compromising the cardiac output. That particular exercise is not one that you see unless you choose to effect it. To be inclined to effect it, you have to be a little convinced of the answer to the question that David (Dantzker) asked, "How do you know it works?" Until it is demonstrated in a prospective, randomized trial, nobody knows it works, but in the meantime, why not do what you do with your patients in cardiogenic pulmonary edema? You seek the lowest wedge pressure that'll give them an adequate cardiac output. So, I'm not saying anything too dramatic here. I'm saying if you want to treat low pressure edema, here, look at 8 animal studies that reduce it by 50% in 4 hours, or 4 clinical studies that do likewise, all with an adequate D_{O_2}. That'll reduce the edema. Now is less edema good? We can argue a lot about whether less edema is good. That has to do with the survivorship characteristics. Is less edema bad? Sure is—if you get less edema by making an inadequate cardiac output. But I want to emphasize that there's nothing in this approach that allows an inadequate cardiac output, and there's nothing in a maximized D_{O_2} approach that assures that the cardiac output is any more than adequate. Did I answer your middle question? I kind of forgot it. I got your euphemism, and I got the business of the transmural pressures. Was there something in the middle? Yes, your patient requiring 139 L of fluid to maintain adequate circulating volume despite a high wedge pressure is a special problem where I look for drainable third spaces (ascites, pleural and pericardial effusions) or excess PEEP, all squeezing the heart. More commonly, I see intensivists create this clinical scenario

by inducing hypervolemia in patients with AHRF in their attempts to maximize D_{O_2}—as the edema increases, so does the PEEP to maintain arterial saturation.

Morris: I had some concern about the resting metabolic rate. You mentioned it. I actually looked up our data to see what our average oxygen consumption was in a large number of patients, and ours is much closer to what Dave (Dantzker) mentioned; so, I'm interested in whether we're dealing with either a different population of presenting illnesses or a different process that presents the ICU team with a different set of unique conditions.

Wood: I don't think either of those is the answer. What you saw is what I introduced, a schematic diagram that shows you what a combination of factors can do at a point in time to a patient's oxygen consumption. The hypothetical patient that I presented was febrile and breathing vigorously, was hypermetabolic due to sepsis, trauma, and burns, and so had a very large oxygen consumption rate.

Morris: Oh, I see. Well, this was not, then, meant to be a representative construction of a population?

Wood: This is meant to illustrate the common phenomenon that patients who have elevated oxygen consumptions, for those reasons, require more D_{O_2} even when they experience no defect in tissue O_2 extraction.

Morris: I'm sorry. I misunderstood. Thank you.

Phang: I want to ask the pathophysiology question again, and your thoughts of trying to reconcile what may be a problem in microcirculation induced by a generalized septic or inflammatory state that's observed in some of your data.[1,2] I actually do think that those data show that there is a problem with the peripheral tissue's extracting oxygen. If I understood correctly, you said that you don't think that there is an extraction problem by human tissue in sepsis.

1. Nelson DP, Beyer C, Samsel RW, Wood LDH, Schumacker PT. Pathological supply dependence of O_2 uptake during bacteremia in dogs. J Appl Physiol 1987;63(4):1487-1492.
2. Nelson DP, Samsel RW, Wood LDH, Schumacker PT. Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxemia. J Appl Physiol 1988;64(6):2410-2419.

Wood: Again, Terry, that's a good question. What I tried to convey is that if one pays attention to the things that we know—raising the circulating hematocrit, raising the cardiac output, and raising the arterial saturation will increase D_{O_2}, and lowering hypermetabolic oxygen consumptions will lower the oxygen consumption—that combination will get the patient more resuscitated in the acute resuscitation phase. What I then said is that I put a question mark on whether there is a peripheral maldistribution problem in patients, as has been shown in animals; even if that's not the mechanism, there certainly is an extraction defect in endotoxin-treated animals. Because I haven't seen any data that support such a pathologic supply-dependence in patients with acute hypoxic respiratory failure, or even in septic shock, I don't choose to extrapolate that canine phenomenon and data in terms of constructing a therapeutic approach for patients. Maximizing the D_{O_2} in order to treat an alleged tissue hypoxia in patients with a pulmonary vascular leak seems to have a lot of down sides to it.

Phang: I agree wholeheartedly with you that the goal for resuscitation should not be to some arbitrary level of cardiac output or whole-body D_{O_2}. Rather, to the best of our ability we should aim to resuscitate patients to ensure that there is no ongoing ischemia at the whole-body, organ, or tissue level. Whether these agents that may affect the microcirculatory shunt and the oxygen extraction defect will prove to be of benefit in the long run in terms of survival, I don't know. These are the anti-inflammatory agents that you mentioned this morning, Len (Hudson). These anti-inflammatory agents do improve physiologic end points of blood pressure and pulmonary artery pressure. But, again, I don't know if they will in the end improve survival.

Wood: And how would you find out if you don't have a reliable index of what anaerobic metabolism is? We don't have an anaerobic 'metabolometer' yet. It's being discussed in this conference, and that's why it keeps coming up. If you take lactic acid away from me, I don't know what to do at the bedside to detect anaerobic metabolism. I've got some clues about how to detect prerenal oliguria; I've got a few clues about detecting central nervous system dysfunction, maybe even a little bit about gut dysfunction, but if elevated blood lactic acid does not tell me that the patient's anaerobic, because it might be due to accelerated aerobic glycolysis and impaired PDH kinase, then I'm left with clinical indicators of adequate perfusion and oxygenation, which are not good enough to answer your question.

Phang: If you attend very closely to your patients and you are vigilant so that to the best of your ability you are assured that there is no ongoing tissue or organ ischemia, what then causes this syndrome of multiple organ system failure?

Wood: What a good question. I mean, that's the question that David (Dantzker) asked right at the start of this, and what does cause multiple system organ failure? And does maximizing the D_{O_2} prevent it? And does getting the patient off the ventilator earlier prevent it? Those are the questions that haven't been answered yet.

Dantzker: May I ask you just one question. Not because I think you have an answer (because I think you don't), but because I think it brings up the whole question that we're dancing around. Let's take a simple thing like hematocrit. If you go to Europe, for example, you would talk to a lot of people who believe that the optimum hematocrit is low. There are good data—experimental data, for example, with the heart—to suggest that under certain circumstances, especially hypotension, that the anemic heart, or the heart being perfused with anemic blood, maintains oxygen consumption better during hypotension than does the heart with normal hematocrit.[1] There is a monograph written about hemodilution in this setting.[2] Now we measured D_{O_2}, and you can easily measure that if you increase hemoglobin, then D_{O_2} will go up. But I think we have no data to suggest that that does anything to a peripheral delivery of oxygen or the adequacy of peripheral delivery of oxygen. I think that being intuitive about it, while it seems to make sense, may not really be very helpful in this situation. That's why I'm always loath when my residents ask, What hemoglobin should you keep? I told the story before about Truman who said that he'd like to find a one-handed economist so that the guy couldn't always say "but on the other hand...." I would say the same thing, well, you know it could be about 30, but, on the other hand, it might..., but I don't have any answers, so I do a lot of hand waving, I'm not sure that 15 grams is a good amount of hemoglobin. I don't think anybody else is, either.

1. Jan KM, Heldman J, Chien S. Coronary hemodynamics and oxygen utilization after hematocrit variations in hemorrhage. Am J Physiol 1980;239: H326-H332.
2. Tuma RF, White JV, Messmer K. The role of hemodilution in optimal patient care. Munich: W Zuckschwerdt Verlag, 1989.

Wood: 35% is my target hematocrit.

Morris: I knew you'd have an answer.

Wood: All the points that you make are right, and you meant them to apply to many of the other struts in the intuitive approach to a complicated patient with acute hypoxic respiratory failure and hypermetabolism. That's why we're talking about this, because I've been with some of you in intensive care units where you don't bat an eye or hesitate in terms of what to do in integrating how you're going to do this with a patient. What we have here is the luxury of trying to ponder and consider whether we have any reason for doing those things. Some people have said that the harder we look at every single thing we're talking about, the less reason we have for doing it. But it hasn't diminished the confidence with which any of you have dealt with patients with these problems. That's why I say 35 is the target hematocrit. And I'll push it. It's always fun to talk about these things because you get more data, and I haven't read the German thesis that says that hemodilution is effective, but when my patient with myocardial ischemia comes in with a hematocrit of 20, he doesn't get diluted. The reason for that is...

Dantzker: Now you're sounding like a surgeon.

Wood: Kiichi Sagawa did this.[1] He showed that as you progressively drop the coronary flow or the hematocrit, you put the heart into oxygen supply-dependent anaerobic metabolism. Keith Walley did it with progressively dropping the F_{IO_2} and showing that the heart develops systolic dysfunction due also to O_2 supply-dependence and a myocardial metabolic limit on pumping function when the arterial O_2 saturation approaches 70%,[2] all in accord with everything that you said over the years about providing an adequate D_{O_2}. So we could talk about this a little more and still get 35 as the target hematocrit.

1. Sunagawa K, Maughan WL, Friesinger G, Guzman P, Chang MS, Sagawa K. Effects of coronary arterial pressure on left ventricular end-systolic pressure-volume relation of isolated canine heart. Circ Res 1982;50:727-734.
2. Walley KR, Becker CJ, Hogan RA, Teplinsky K, Wood LDH. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. Circ Res 1988;63:849-859.

Morris: The way, in my opinion, to get at what we ought to do is to deemphasize our interest in the conceptual validity of what we decide and focus on operational definitions, recognizing that no operational definition for the purpose of making decisions will be ideal, but it will be defined. I'd like to get back to that because I think many of the things that have been discussed in the last 15 minutes fall back into this dilemma—where we confuse conceptual validity with the operational definition necessary to make decisions. I'm very interested in what you've said, because it sounds to me like you've got all of the elements for constructing an operational definition for everybody in this room.

Wood: Would "seek the lowest wedge pressure that provides an adequate D_{O_2}" be operational?

Dantzker: It could be.

Morris: Well, let me ask you this. If I told you the operational definition for finding a satisfactory mate was to pick an attractive woman who agreed with your basic ideas, would that be adequate? The test of whether it's adequate is whether you can get a third party—could you get Len Hudson, with that rule, to go out to another room and pick a mate who would serve him well for the next 50 years?

The answer is obvious. If you tell me the operational definitions that provide satisfactory D_{O_2}, can we get a good resident in your service to go to another hospital and clearly define it by phone. If the answer is no, then I suggest that that is not a satisfactory operational definition because it cannot be used to actually execute any action.

Wood: That's a very good answer, and I agree with everything you said, but *I can* do that.

Morris: Yeah, but if what you mean by "I can do that" is what I think you mean—that's why I'm so interested in what you said.

Wood: I can do that, a piece of cake.

Morris: Because it seems to me as if you have all of the elements for actually constructing an operational definition, and if Dr Cerra has the complement, then we have all of the ingredients for finding out whether one of these techniques is better or worse than the other.

Wood: I can't wait.

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Oxygen Transport: Does Increasing Supply Improve Outcome?

Michael D Pasquale MD, Mark D Cipolle MD, and Frank B Cerra MD

I. The Role of Oxygen
II. Delivery of Oxygen—The Supply Side
III. Consumption of Oxygen—The Demand Side
IV. Pathologic Oxygen Supply-Dependency—Does It Exist?
V. Should Systemic Oxygen Delivery Be Elevated?
VI. How To Augment Oxygen Delivery
VII. Summary

The Role of Oxygen

The major source of adenosine triphosphate (ATP) in aerobic organisms is oxidative phosphorylation. When glucose is completely oxidized to water and carbon dioxide, 36 ATP molecules are formed if the glycerol phosphate shuttle is used to bring electrons from cytosolic NADH to the mitochondrial respiratory chain (38 ATP if the malate-aspartate shuttle is used), and 12 molecules of oxygen are consumed. Most of the ATP, 32/36 or 34/38, are generated by oxidative phosphorylation (Fig. 1). In this process, electrons from the energy-rich molecules (ie, reduced form of oxidized nicotinamide-adenine dinucleotide, NADH, and reduced form of flavin adenine dinucleotide, $FADH_2$) formed during glycolysis, fatty acid oxidation, and via the citric acid cycle, are donated to molecular oxygen. In this transfer, a large amount of free energy is produced, which is used to generate ATP. The oxidation of NADH and $FADH_2$ and subsequent phosphorylation to produce ATP are coupled by a proton gradient (proton-motive force)

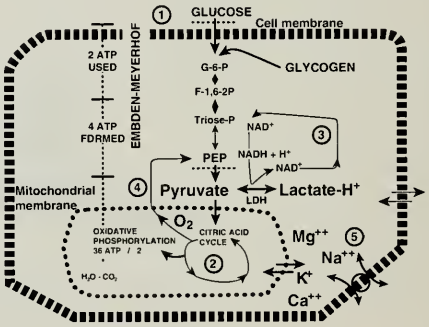

Fig. 1. Cellular glucose metabolism, lactic acid production, and ATP generation. 1—The cells are often mainly dependent on endogenous sources of substrate due to a trauma-induced insulin resistance impairing glucose uptake. 2—Glycolysis proceeding to complete oxidative phosphorylation results in the production of 36 mols of ATP per mol glucose as compared to only 2 mols of ATP during anaerobic metabolism. 3—Regeneration of NAD^+ is necessary for the glycolytic process to proceed during tissue anaerobiosis. This is achieved by LDH-regulated transfer of H^+ onto pyruvate in the formation of lactic acid. 4—The energy-requiring process of gluconeogenesis is inhibited in the absence of oxygen. 5—Intracellular accumulation of protons and energy failure alters the membrane permeability to ions and the functional capacity of ion pumps, which is seen as a reduced cellular transmembrane potential (MP) level.

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Key to Abbreviations and Symbols

ADP	—	adenosine diphosphate
ARDS	—	adult respiratory distress syndrome
ATP	—	adenosine triphosphate
C_{aO_2}	—	arterial O_2 content
$C_{(a-\bar{v})O_2}$	—	arteriovenous O_2 content difference
CI	—	cardiac index
COPD	—	chronic obstructive pulmonary disease
CVP	—	central venous pressure
D_{O_2}	—	oxygen delivery
$D_{O_{2crit}}$	—	critical oxygen delivery
D_5LR	—	5% dextrose in lactated Ringer's solution
D_5-0.5NS	—	5% dextrose in half-normal saline
D_5W	—	5% dextrose in water
$FADH_2$	—	reduced form of flavin adenine dinucleotide
F_{IO_2}	—	fractional inspired oxygen concentration
LR	—	lactated Ringer's solution
NAD^+	—	oxidized nicotinamide-adenine dinucleotide
NADH	—	reduced form of NAD
NADH-Q	—	reduced form of NAD where Q = ubiquinone
NS	—	normal (0.9%) saline
NT	—	normal treatment group
OT	—	optimal treatment group
P_{aO_2}	—	arterial oxygen tension
P_{pcw}	—	pulmonary capillary wedge pressure
PEEP	—	positive end-expiratory pressure
PFK	—	6-phosphofructokinase
P_i	—	inorganic phosphate
PVR	—	pulmonary vascular resistance
RR	—	respiratory rate
S_{aO_2}	—	arterial oxygen saturation
SBP	—	systolic blood pressure
SVR	—	systemic vascular resistance
$\dot{V}_{O_2}$	—	oxygen consumption

that is generated across the inner mitochondrial membrane. The proton-motive force is an interconvertible form of free energy that can be utilized for ATP synthesis, adenosine diphosphate (ADP)-ATP exchange, and energy-dependent transport and osmotic exchange. The driving force of oxidative phosphorylation is the electron-transfer potential of NADH or $FADH_2$ relative to that of oxygen. This transfer occurs through a chain of three large-protein complexes (NADH-Q reductase, cytochrome reductase, and cytochrome oxidase) situated on the inner mitochondrial membrane (Fig. 2).

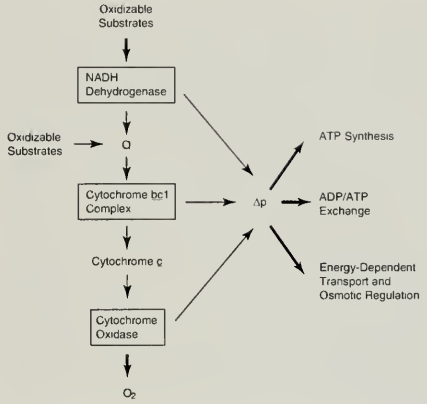

Fig. 2. Regulation of mitochondrial function. Control exists at several sites, as indicated by the bold arrows. Control of NAD^+-linked dehydrogenases regulates the reductive force available from the NADH/NAD^+ couple. Together with control of cytochrome oxidase, these regulate the amount of energy available from oxidation for maintaining the proton-motive force (Δp). Utilization of Δp for ATP synthesis, ADP/ATP exchange across the inner membrane, and osmotic processes are also under independent regulation.

Oxidative phosphorylation requires a source of electrons at high potential (NADH, $FADH_2$), oxygen, ADP, and inorganic phosphate (P_i). The most important factor in determining the rate of oxidative phosphorylation is the level of ADP. The rate of oxygen consumption by tissues ($\dot{V}_{O_2}$) increases markedly when ADP is added and then returns to its initial value when the added ADP has been converted into ATP. Note that if the proton-motive force of the inner mitochondrial membrane is dissipated, respiratory control is lost and oxidative phosphorylation is uncoupled. This leads to an increase in $\dot{V}_{O_2}$ and oxidation of NADH. Thus, a reduction in ATP production can occur for a variety of reasons, including lack of oxygen, a primary interruption of the proton-motive gradient, low ADP, or the level of P_i availability.

Under conditions in which oxygen deficiency occurs, electron flow to oxygen becomes impaired. Without input of the energy for the oxidative reactions, utilization of the proton-motive force for ATP production and subsequent hydrolysis of ATP by the cell result in a dissipation of the proton-

motive force. Such dissipation leads to osmotic, ionic, and acid-base imbalances within the cell and eventually progresses to irreversible cell injury and cell death. Under hypoxic/anoxic conditions, the proton-motive force must be maintained by an alternate energy source such as ATP from glycolysis or by inhibition of ion conductance so that the force is lost slowly. It has been observed that ATP from glycolysis was not used to maintain the proton-motive force during anoxia, but, rather, a selective regulation of ion transport across the mitochondrial inner membrane occurred.[1] This anoxic regulation results in an inhibition of ATP synthase and hence a decrease in ATP production despite having sufficient proton-motive force for ATP synthesis.[1,2] By this mechanism, proton-motive force is preserved.

When tissue perfusion is critically reduced, the availability of oxygen and of exogenous substrate becomes reduced. The only substrate that can be used for energy without utilization of oxygen is carbohydrate. Thus, tissue cells are mainly dependent on glycolytic metabolism in hypoxic situations. Anaerobic glycolysis proceeds in the cells mainly via the Embden-Meyerhof pathway in the cytosol (Fig. 3). The pace of glycolysis is controlled by the activities of three functionally unidirectional enzymes that catalyze rate-limiting, nonequilibrium steps in an irreversible mode: hexokinase, 6-phosphofructokinase (PFK), and pyruvate kinase (Fig. 3). ATP is an allosteric inhibitor of the PFK reaction, and when ATP stores are reduced, flux through this reaction is augmented and the rate of glycolysis is increased. A key step in glycolysis is the oxidation of glyceraldehyde-3-phosphate, during which oxidized nicotinamide-adenine dinucleotide (NAD^+) is consumed and converted to NADH (Fig. 3). Provision of NAD^+ is therefore essential to the maintenance of glycolysis. Anaerobic tissues under normal conditions and aerobic tissues under hypoxic conditions replenish NAD^+ stores by the cytosolic conversion of pyruvate to lactate (Fig. 4). Aerobic tissues under normal conditions regenerate NAD^+ via mitochondrial oxidative reactions. This oxidation process requires transmitochondrial shuttles (glycerol phosphate, malate/aspartate) and results in effective transport of hydrogen ions across the mitochondrial membrane and the reoxidation of cytosolic NADH.

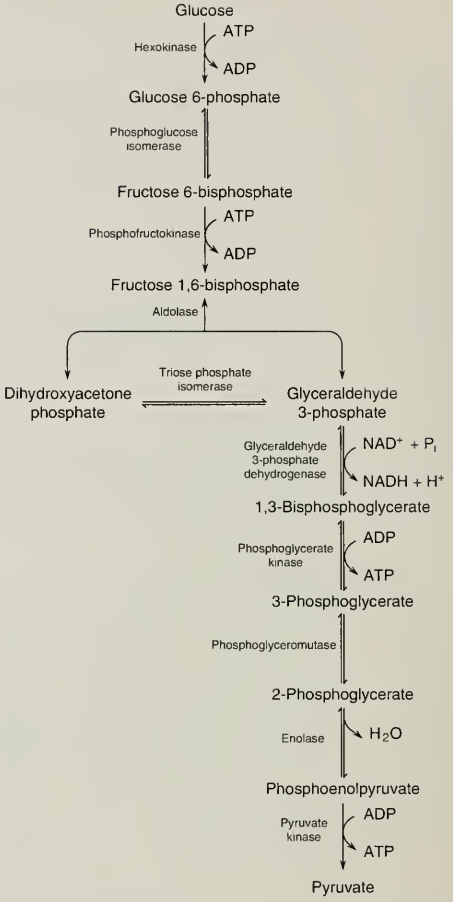

Fig. 3. The glycolytic pathway.

Consumption of pyruvate in aerobic tissues under normal conditions occurs by means of two oxidative mitochondrial pathways and follows the transport of pyruvate across the mitochondrial membrane. The first pathway is oxidative decarboxylation to acetyl-coenzyme A (catalyzed by pyruvate dehydrogenase) in a reaction that requires a continuous supply of NAD^+ (Fig. 4). The second pathway is gluconeogenesis, which occurs exclusively in the liver and the renal cortex (Fig. 4). The conversion of one molecule of glucose to pyruvate

or lactate is associated with the net production of two molecules of ATP. As mentioned previously, the subsequent aerobic oxidation of pyruvate generates an additional 34 or 36 ATP, depending on the shuttle used.

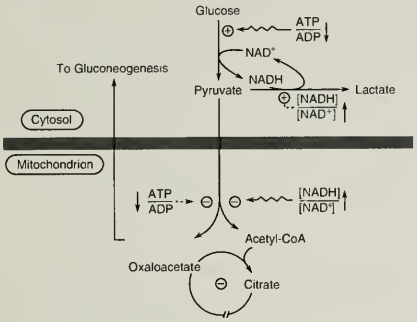

Fig. 4. Mechanism of hypoxia-induced accumulation of lactate.

In hypoxic situations, impaired mitochondrial oxidative function leads to accumulation of pyruvate in the cytosol and thus to increased lactate production. The accumulation of pyruvate reflects both overproduction and reduced utilization of pyruvate through its two pathways. Pyruvate accumulates because a decreased supply of ATP to the cytosol stimulates the PFK reaction and results in augmented glycolysis. During anaerobic conditions, glycolysis becomes the main source of energy and, despite the prevailing mitochondrial dysfunction, continuation of glycolysis is assured by cytosolic regeneration of NAD^+ via the conversion of pyruvate to lactate. With a decrease in oxygen, there is reduced availability of NAD^+ within the cytosol that alters the redox potential of the cell with an increased NADH-NAD^+ ratio. This shifts the equilibrium of the lactate dehydrogenase reaction toward lactate. Thus, under conditions of tissue hypoxia, stimulation of glycolysis leads to augmented lactic acid production and a resultant decrement in intracellular pH. This is reflected in an excess of lactate relative to pyruvate and a lactate-pyruvate ratio that increases. This acidosis occurs secondarily to the hydrolysis of ATP, which leads to the generation of free hydrogen ion.

Most lactate utilization is via oxidation back to pyruvate. The liver and renal cortex are the major lactate-consuming organs and can use lactate (via pyruvate) as a substrate for gluconeogenesis or oxidize it to carbon dioxide and water. Cardiac muscle can directly oxidize lactate utilizing the malate-aspartate shuttle. Under hypoxic conditions, however, the liver can release lactate into the blood.[3,4] In view of the fact that both pathways of lactate utilization depend critically on intact mitochondrial function, it is not suprising that tissue hypoxia produces defective lactate processing.[5]

Hence, when the availability of oxygen becomes limited, oxidative phosphorylation decreases and the process of glycolysis increases. The small amounts of ATP generated by this process are not sufficient to cope with the energy needs of most tissues and lead to the risk of cellular energy failure. The duration of hypoxia that is tolerated depends on the metabolic requirements of the tissues affected. Also, in conditions of decreased oxygen availability, lactate and hydrogen ion increase because consumption of these products via oxidation and/or gluconeogenesis cannot effectively proceed. The increased intracellular hydrogen ion activity and impaired energy production of glycolysis cause a derangement in function of the cellular membrane pumps. Normal ionic gradients can no longer be maintained, and increased leakage occurs. As mentioned before, this causes a dissipation of the transmembrane potential, cellular dysfunction, and finally cellular death.

In systemic inflammatory states such as soft-tissue injury or infection with sepsis, an alternate form of aerobic energy production occurs, that of aerobic glycolysis, provided that adequate resuscitation has occurred. This biochemical process appears as efficient as aerobic metabolism with normal cytosolic and mitochondrial redox potentials. It is characterized by the decreased oxidation of pyruvate, an active Cori cycle with recycling of lactate and alanine, increased plasma lactate and/or lactate turnover and normal lactate-pyruvate ratio, and increased oxidation of fats and amino acids in the Krebs cycle.[6]

Delivery of Oxygen—The Supply Side

In order to keep pace with metabolic demands, the transport of oxygen to tissues requires the integration of the lungs, the circulation, and the blood. The lungs normally load approximately 4

mL of $O_2 \cdot min^{-1} \cdot kg^{-1}$ of body mass onto hemoglobin (Hb) but are capable of increasing this about 15 times.[7] The cardiovascular system affects oxygen supply through variation in the cardiac output (C.O.) and the internal distribution of blood flow. The basal C.O. of 3-4 $L \cdot min^{-1} \cdot m^{-2}$ may increase about five times with stress. The major determinant of this output is metabolic demand, which acts by local vasodilation to increase blood flow and venous return.[7-9] Blood viscosity and volume are additional determinants of C.O. If volume is held constant and viscosity is altered by a change in hematocrit, a reciprocal change in C.O. occurs.[10] C.O. changes in the same direction as blood volume via an increase in venous return. The distribution of blood flow serves the oxygen needs of different tissues. With a decrease in oxygen availablility, flow decreases in tissues with low extraction in favor of tissues with high extraction.[7,11] The high-flow, low-extraction areas of the circulation, then, constitute an oxygen reserve.

Hemoglobin concentration is regulated by a renal sensing mechanism such that any decrease in concentration or arterial oxygen saturation (S_{aO_2}) of hemoglobin, or any increase in hemoglobin affinity for oxygen, causes increased erythropoietin production.[12] The affinity of hemoglobin for oxygen, in concert with flow distribution, translates blood flow into available oxygen. As the oxygen tension at which 50% of hemoglobin is saturated (P_{50}) increases, there is a lower affinity of hemoglobin for oxygen, whereas a decreased P_{50} corresponds to a higher affinity.[13] Any change in the position of the oxygen dissociation curve profoundly affects the amount of oxygen available at normal tissue oxygen tensions, whereas oxygen uptake by hemoglobin is little affected.

To summarize, then, the delivery of oxygen to tissues depends upon the perfusion rate and the concentration of oxygen in the perfusing medium. The regulated variable seems to be the maintainance of the 'free' oxygen gradient between the capillary and the cells. Maintaining this gradient requires the integration of the lungs via oxygen tension, the circulation via C.O., and the blood via hemoglobin concentration and affinity for oxygen. Oxygen delivery may be defined, then, by the product of cardiac index (CI) and arterial oxygen concentration:

$$\text{Oxygen delivery} = \text{cardiac index} \times \text{arterial oxygen content.}$$
$$D_{O_2} = (CI)\,(C_{aO_2}).$$
$$D_{O_2} = (CI)\,[(1.34)(Hb)(S_{aO_2}) + (0.003)(P_{aO_2})].$$

Consumption of Oxygen—The Demand Side

Depending on the oxygen needs of the tissue, a variable amount of oxygen is extracted from that which is delivered. The actual amount of oxygen that is consumed by the tissue can be calculated if the flowrate and arteriovenous oxygen content difference are known:

$$\text{Oxygen consumption} = (\text{cardiac index})\,(\text{arteriovenous oxygen content difference}), \text{ or}$$
$$\dot{V}_{O_2} = (CI)\,[C_{(a-\bar{v})O_2}].$$

The $\dot{V}_{O_2}$, then, is an indirect assessment of the tissue's oxygen demand. There is no current, clinically useful method to directly measure how much oxygen a tissue would like to consume under a given set of conditions. This limitation has been and continues to be a major factor in the evaluation of supply-dependency states.

If the tissue oxygen demand increases, it may extract more oxygen from the blood without requiring any additional blood flow. Graphically, if $\dot{V}_{O_2}$ is plotted against D_{O_2}, the slope of the line from any point through the origin of the graph defines the oxygen extraction ratio, ie, $C_{(a-\bar{v})O_2}/C_{aO_2}$ (Fig. 5). This variation in the oxygen extraction ratio ($\dot{V}_{O_2}/D_{O_2}$) is modulated at the microcirculatory level by recruitment of effective capillary surface area, maintaining the 'free' oxygen gradient between the capillary and the cell, and at the mito-

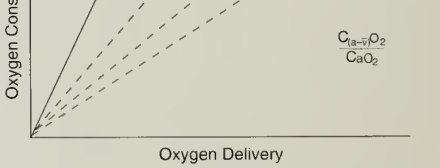

Fig. 5. Oxygen consumption plotted against oxygen delivery. Note that the slope of the line drawn from any point on the curve corresponds to the oxygen extraction ratio as defined by the equation $m = C_{(a-\bar{v})O_2}/C_{aO_2}$.

chondrial level by alteration in the mitochondrial substrate.[14-17] As oxygen demand increases further, however, extraction ratios approach a maximum, and tissue blood flow must increase to provide adequate supply. Under normal conditions, this maximum extraction ratio has been found to be approximately 0.7 (Fig. 5).[18] This is referred to as macrovascular regulation and involves redistribution of whole-body D_{O_2} among organs and/or increases in C.O. It has been shown that as whole-body oxygen decreases, the fraction of C.O. distributed to dermal, renal, and splanchnic beds declines, while the fraction of C.O. distributed to the brain and myocardium increases.[7,19,20] Thus, redistribution of whole-body D_{O_2} promotes macrovascular oxygen regulation by reducing perfusion of organs that are normally overperfused relative to need. Schlichtig et al[21,22] have shown that redistribution of whole-body D_{O_2} among organs facilitates whole-body oxygen regulation, and this in turn increases oxygen utilization of the whole organism.

Once these compensatory mechanisms have been fully utilized, tissue extraction of oxygen reaches a maximum. Further increases in metabolic demand then result in an oxygen debt—ie, oxygen supply does not meet demand. The point at which oxygen utilization becomes dependent upon the D_{O_2} is referred to as the point of critical oxygen delivery (D_{O_2crit}) (Fig. 6).[18] When D_{O_2} falls below this

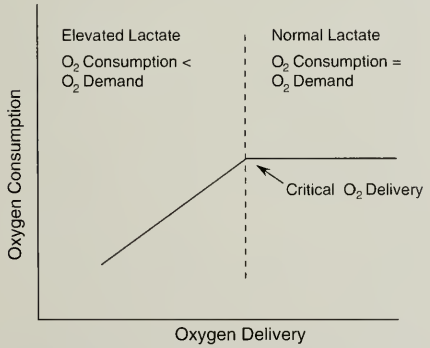

Fig. 6. The physiologic oxygen consumption-delivery relationship. Flow-dependent oxygen consumption is shown to the left of the critical oxygen delivery, while flow-independent oxygen consumption occurs to the right of this point.

critical value, the $\dot{V}_{O_2}$ is dependent upon supply; whereas above this critical value, $\dot{V}_{O_2}$ is said to be supply-independent (Fig. 6). In a study of dogs that were subjected to anemia and hypoxic forms of hypoxia,[23] D_{O_2crit} was 9.8 mL · min^{-1} · kg^{-1}. In a study conducted by Shibutani et al,[24] looking at the relationship between D_{O_2} and $\dot{V}_{O_2}$ in preoperative cardiac surgery patients, D_{O_2crit} occurred at 330 mL · min^{-1} · m^{-2} or 8.2 mL · min^{-1} · kg^{-1} (Fig. 7). This supply-dependence has been shown not only on a global level but also in individual organ systems (Fig. 8).[22,24,25]

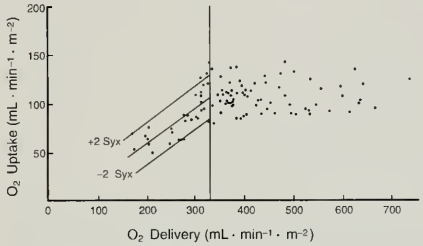

Fig. 7. Relationship between oxygen delivery and oxygen consumption (uptake) based on 99 sets of measurements in 58 patients. The line is a linear regression calculated from the datapoints where oxygen delivery was less than 330 mL · min^{-1} · m^{-2}. (From Reference 24, with permission.)

With decreased oxygen availability, oxidative phosphorylation becomes less efficient and glycolysis increases.[25,26] This, in turn, leads to an accumulation of lactate and, possibly, metabolic acidosis. Cain[27] noted a correlation between true oxygen deficit and peak excess lactate concentrations in dogs subjected to hypoxia (Fig. 9). Simmons et al[28] noted marked increases in lactate when D_{O_2} was reduced by > 50%. Fahey and Lister[29] noted that in conscious lambs, as $\dot{V}_{O_2}$ became D_{O_2}-dependent, lactic acidosis occurred. Lastly, Waxman et al[30] demonstrated a correlation between increased serum lactate concentrations and decreased $\dot{V}_{O_2}$ in the perioperative period of 12 general surgical patients.

To summarize, then, the essential elements to achieve high oxygen extraction in the periphery are perfusion and recruitable capillary reserve. In an otherwise intact animal that can maintain or increase C.O., any prolonged decrease in oxygen supply severe enough to limit $\dot{V}_{O_2}$ results in an increase

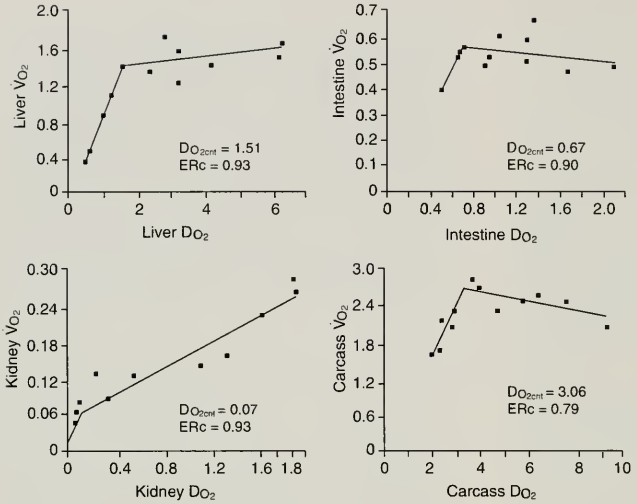

Fig. 8. Relationship between $\dot{V}O_2$ and D_{O_2} of liver, intestine, left kidney, and carcass of a dog. Regression lines, critical delivery ($D_{O_{2crit}}$), and critical oxygen extraction ratio (ERc) are included on each plot. (From Reference 22, with permission.)

in oxygen extraction. When no further increase in extraction is possible, $\dot{V}O_2$ becomes dependent upon D_{O_2}, oxygen debt accrues, and lactate production increases.

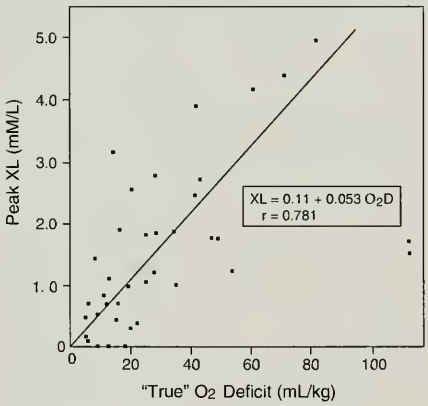

Fig. 9. Relationship of true oxygen deficit to peak excess lactate value (XL) obtained for that period of hypoxia. (From Reference 27, with permission.)

Pathologic Oxygen Supply-Dependency—Does It Exist?

In some critically ill patients, supply-dependency of $\dot{V}O_2$ has been observed at levels of D_{O_2} that are normally considered adequate.[15] That is to say, at increased levels of tissue demand, the demand is met by increased oxygen supply in the presence of a reduced maximum extraction ratio, referred to as pathologic supply-dependency. Thus, two components of supply-dependency exist at any given level of demand—the amount of oxygen delivered and the extraction ratio. Physiologic supply-dependency refers to a reduction in D_{O_2}, whereas pathologic supply-dependency refers to inefficient oxygen extraction. The difference is reflected in the point of $D_{O_{2crit}}$ and the slope of the $\dot{V}O_2$-D_{O_2} curve, ie, the extraction ratio (Fig. 10). By definition, this concept assumes that increased oxygen demands are not being met and that a defect exists in oxygen supply and/or the physiologic mechanisms that enable tissues to increase their oxygen extraction as D_{O_2} is lowered. Under physiologic conditions, as oxygen supply is reduced, microvascular regulation, via capillary recruitment, is able to oppose neurally and humorally mediated vasoconstriction.[31,32] This results in decreased perfusion to nonessential organs.[31,32] When this ability is lost, oxygen demand is not met, cellular hypoxia exists, and the $D_{O_{2crit}}$ is increased.[33] Loss of the ability to recruit effective capillary surface area, whether it be from inadequate flow or via leukocyte plugging, membrane damage by free oxygen

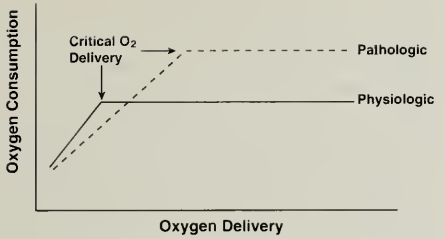

Fig. 10. Physiologic versus pathologic oxygen consumption-delivery relationship. Note that the critical oxygen delivery occurs at a higher oxygen delivery than under physiologic conditions. The slope of the pathologic consumption curve below the critical oxygen delivery point reflects the decrease in the oxygen extraction ratio that exists in such situations.

radicals, or loss of endothelium-derived vascular control, results in effective lengthening of the pathways for oxygen diffusion. This recruitment failure is reflected in a reduction in the extraction ratio. An increase in D_{O_2} is then required to raise capillary P_{aO_2} and overcome the diffusion resistance.[34]

Although the $\dot{V}_{O_2}$-D_{O_2} relationships under physiologic conditions are well established, the existence of pathologic oxygen supply-dependency is controversial. Most of the data regarding this subject have been obtained in septic animal models and in patients with adult respiratory distress syndrome (ARDS).

Nelson et al[16] demonstrated pathologic supply-dependence in dogs that underwent continuous infusion of *Pseudomonas aeruginosa*. The mean $D_{O_{2crit}}$ in the bacteremic group (11.4 ± 2.2 mL · min^{-1} · kg^{-1}) was significantly higher than the mean value for the control group (7.4 ± 1.2 mL · min^{-1} · kg^{-1}) ($p < 0.05$) (Fig. 11). The mean (standard deviation) of the corresponding oxygen extraction ratio at the critical point of the control group, 0.71 (0.10), was significantly higher ($p < 0.05$) than that of the bacteremic group, 0.51 (0.09). Also, the $D_{O_{2crit}}$ from the point at which lactic acid concentration began to increase was significantly higher in the bacteremic group, 11.2 (2.0) mL · min^{-1} · kg^{-1} than in controls, 9.1 (1.3) mL · min^{-1} · kg^{-1} ($p < 0.05$) (Fig. 11). The authors concluded by suggesting that relative maldistribution of blood flow within the organ systems relative to organ oxygen demand produces abnormal oxygen supply-dependency. In the hypoperfused tissues, $\dot{V}_{O_2}$ becomes limited by molecular diffusion as end-capillary P_{aO_2} reaches a critical level. In contrast, the hyperperfused areas

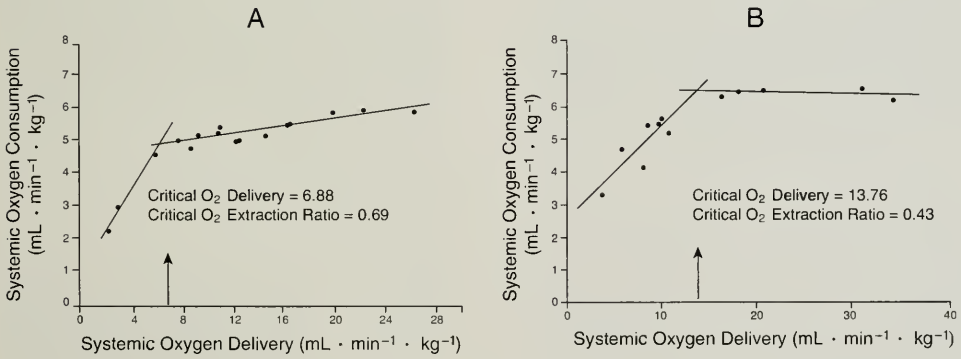
A
Systemic Oxygen Consumption (mL · min^{-1} · kg^{-1})
Critical O_2 Delivery = 6.88
Critical O_2 Extraction Ratio = 0.69
Systemic Oxygen Delivery (mL · min^{-1} · kg^{-1})
B
Systemic Oxygen Consumption (mL · min^{-1} · kg^{-1})
Critical O_2 Delivery = 13.76
Critical O_2 Extraction Ratio = 0.43
Systemic Oxygen Delivery (mL · min^{-1} · kg^{-1})

Fig. 11. Relationship between systemic oxygen consumption and delivery (top) found in a representative control (A) and bacteremic (B) experiment. Critical oxygen delivery was determined from intersection of two lines that best fit the data. The critical extraction ratio was determined as interpolated value at critical oxygen delivery. Lower plots show the relationship between blood lactate concentration and systemic oxygen delivery in same control (A) and bacteremic (B) experiments. Critical oxygen delivery by lactate analysis, defined as the delivery below which lactate concentration increased, was also determined as intersection of two lines that best fit data. (From Reference 16, with permission.)

with a low oxygen demand demonstrate a low extraction ratio at the D_{O_2crit} point.

Samsel et al[35] displayed pathologic supply-dependence in a group of dogs undergoing endotoxin infusion. The D_{O_2crit} for endotoxemic animals was 11.4 (2.7) $mL \cdot min^{-1} \cdot kg^{-1}$ vs 8.0 (0.7) $mL \cdot min^{-1} \cdot kg^{-1}$ for controls ($p < 0.05$) (Fig. 12). Again, the extraction ratio at the critical point was found to be significantly lower in the endotoxin-treated animals, 0.61 (0.11) versus 0.70 (0.07) ($p < 0.05$) (Fig. 12). The authors concluded that endotoxin may set the stage for vascular dysregulation, leaving the tissues unable to optimally distribute blood flow with respect to oxygen demand.

Curtis et al[36] analyzed $\dot{V}_{O_2}$-D_{O_2} relationships in endotoxemic dogs as compared to controls. They found significantly increased ($p < 0.05$) $\dot{V}_{O_2}$ and D_{O_2crit} in hindlimb muscles. They were not, however, able to demonstrate a significant difference in limb critical oxygen extraction ratios between the two groups. This suggests that although oxygen demand was greater in endotoxemic animals, there was no diffusional limitation below the D_{O_2crit} point.

The presence of elevated plasma lactate and lactic acidosis is often used to support the concept of underlying cellular ischemia/hypoxia in pathologic situations. Blood lactate levels have been used to predict pathologic oxygen supply-dependence as well as outcome.[37,38] In situations of limited oxygen availability, lactate is elevated and pyruvate is forced to serve as the hydrogen ion acceptor in place of oxygen. In this setting, excess lactate is present.

In resuscitated inflammatory states, however, aerobic glycolysis is present. Elevated lactate is proportional to pyruvate, cytosol redox is normal, and a stoichiometric relationship exists among lactate, pyruvate, and alanine.[39] The lactate level in this setting is not a reliable predictor of supply-dependency and requires a determination of pyruvate and alanine for its interpretation. This phenomenon may account for the lack of relationship among $\dot{V}_{O_2}$, D_{O_2}, and lactate that has been observed in human studies.

In 1980, Danek et al[40] demonstrated that in 20 patients with ARDS there was a direct relationship between D_{O_2} and $\dot{V}_{O_2}$. In this study, D_{O_2} was changed by changing the level of positive end-expiratory pressure (PEEP). No relationship between increased $\dot{V}_{O_2}$ and increased lactate was noted. Kaufman et al[41] demonstrated that in both hypovolemic and septic groups, increasing D_{O_2} by fluid resuscitation significantly increased $\dot{V}_{O_2}$. Serum lactate levels were found to decrease with augmentation of $\dot{V}_{O_2}$ and D_{O_2}; however, the change was not significant. Haupt et al[42] prospectively evaluated 20 patients with systemic sepsis and signs of circulatory failure to determine whether fluid loading was associated with increases in systemic D_{O_2} and $\dot{V}_{O_2}$ and with decreases in blood lactate levels. They concluded that lactic acidosis was a marker that predicted increases in $\dot{V}_{O_2}$ in septic patients who respond to fluid loading with an increase in D_{O_2}. Bi-

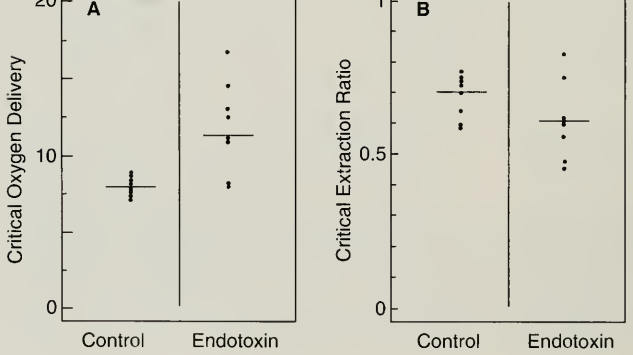

Fig. 12. A. Distribution of critical oxygen delivery for two groups. B. Distribution of critical oxygen extraction ratio for two groups. Both differences are significant by 2-tailed *t* test ($p < 0.05$). (From Reference 35, with permission.)

hari et al[43] hypothesized that inadequate tissue oxygenation may occur in critically ill patients despite the presence of apparently adequate systemic blood flow, pressure, and P_{aO_2}, and that this may contribute to the development of irreversible multiple-organ failure. Using a fixed dose of 5 ng · min^{-1} · kg^{-1} of prostacycline, they conducted an "oxygen flux test" in which the oxygen supply to tissues was increased and the response, in terms of a change in $\dot{V}O_2$, was observed. It was found that the increase in CI induced by the prostacycline infusion was associated with a substantial and significant increase in D_{O_2} to tissues in all patients (median increase of 20%, $p < 0.001$). In nonsurvivors, the increase in D_{O_2} was associated with a significant increase in $\dot{V}O_2$ (median increase of 19%, $p < 0.01$) (Fig. 13-A). Ten of the 13 nonsurvivors also had an increase in the oxygen extraction ratio (median increase of 11%, $p < 0.01$). This was in contrast to survivors, in whom the increase in D_{O_2} resulted in an insignificant increase in $\dot{V}O_2$ and a reduction in the extraction ratio (Fig. 13-B). This suggests that some critically ill patients have a tissue oxygen debt despite an apparently adequate systemic oxygenation and D_{O_2}. In this instance, a vasodilator was used to uncover this debt.

The absence of any change in $\dot{V}O_2$ in survivors confirms that $\dot{V}O_2$ is usually independent of D_{O_2} in healthy patients.[43] Astiz el al[44] analyzed the relationship of increases in D_{O_2} to changes in $\dot{V}O_2$ in 10 patients with hyperdynamic shock (CI > 2.8 L · min^{-1} · m^{-2}). With volume infusion, significant increases in D_{O_2} led to significant increases in $\dot{V}O_2$ and significant decreases in arterial lactate concentrations. This group also noted no change in the oxygen extraction ratio, ie, mean (SD) 0.33 (0.03) to 0.30 (0.01), and suggest that oxygen utilization is perfusion-limited in hyperdynamic septic shock. In a separate prospective study of 50 consecutive patients with sepsis and 50 consecutive patients with acute myocardial infarction (all with blood lactate levels > 1 mMol/L) to determine the critical threshold of D_{O_2} for increased lactate, no threshold was found.[45] In this study, the D_{O_2} ranged from 136 to 811 mL · min^{-1} · m^{-2} in septic patients and from 115 to 434 mL · min^{-1} · m^{-2} in patients with acute myocardial infarction. Hence, supply-dependency of $\dot{V}O_2$ and D_{O_2} existed even at high levels of D_{O_2}, but a critical threshold relationship with plasma lactate was not evident.

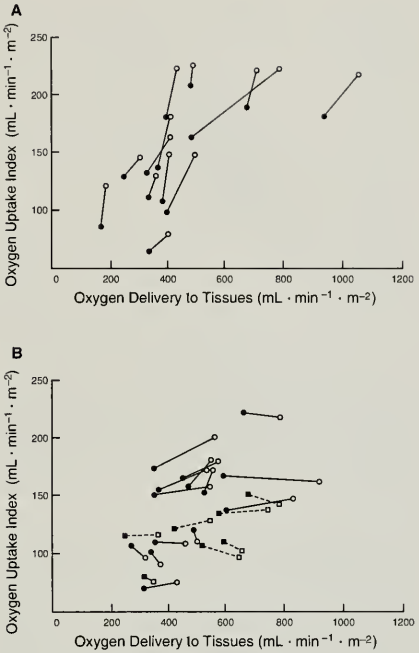

Fig. 13. Oxygen uptake in relation to oxygen delivery in 27 patients with acute respiratory failure and 7 controls, before and during prostacyclin infusion. Patients are represented by circles and controls by squares. Solid symbols denote the values determined before infusion (5 ng · min^{-1} · kg^{-1}), and open symbols denote the values determined at 30 minutes. A. The 13 patients who died had significant increases in oxygen uptake in association with increases in oxygen delivery. B. The 14 surviving patients and the controls had no significant increases in uptake. (From Reference 43, with permission.)

Tuchschmidt et al[46] demonstrated supply-dependency below a $D_{O_{2crit}}$ of 15 mL · min^{-1} · kg^{-1} in medical patients with septic shock (Fig. 14). Below this level, patients developed increased arterial lactate, suggesting that D_{O_2} was inadequate to meet the needs of aerobic metabolism (Fig. 15). In a similar study of patients with ARDS, Mohsenifar et al[47] found that the $D_{O_{2crit}}$ was approximately 21 mL · min^{-1} · kg^{-1}. Shoemaker et al[48] demonstrated flow-dependent $\dot{V}O_2$ in 34 critically ill general surgical patients. Dobutamine was used to augment D_{O_2} in this group of patients, and it was felt that this therapy improved overall flow and flow distri-

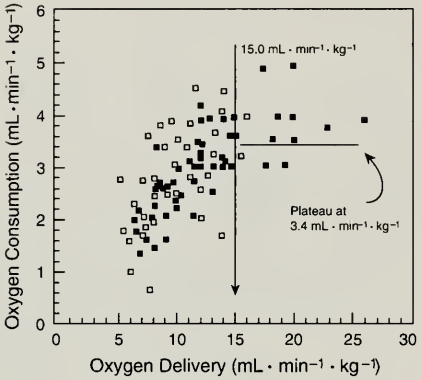

Fig. 14. Medical patients with septic shock were found to have a critical oxygen delivery of 15 mL · min^{-1} · kg^{-1}, with nonsurviving patients all falling below this value after resuscitation. ■ = survivors; □ = nonsurvivors. (From Reference 46, with permission.)

bution, which resulted in increased oxygen utilization and alleviation of tissue hypoxia. In 1990, Vincent et al[49] looked at the possibility of using short-term dobutamine infusion to disclose $\dot{V}_{O_2}$ supply-dependency. Patients with heart failure or sepsis were separated according to their blood lactate levels, ie, greater or less than 2 mMol/L (Fig. 16). Dobutamine infusion at 5 μg · min^{-1} · kg^{-1} resulted in significant increases in C.O. and oxygen transport. $\dot{V}_{O_2}$, however, increased significantly only in patients with elevated blood lactate levels. This study demonstrated that in critically ill patients with coexistent tissue hypoxia as reflected by increased lactate levels, a short-term dobutamine infusion can be used to disclose a $\dot{V}_{O_2}$ supply-dependency phenomenon.

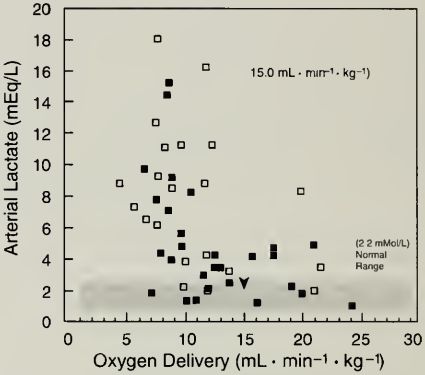

Fig. 15. Arterial lactate levels were observed to increase when oxygen delivery decreased to below 15 mL · min^{-1} · kg^{-1} in medical septic shock patients. ■ = survivors; □ = nonsurvivors. (From Reference 46, with permission.)

Based on these studies, it appears that critically ill patients may have an impaired ability to extract oxygen while also having higher oxygen requirements. More importantly, it appears that critical tissue hypoxia can occur long before the presumed switch from aerobic to anaerobic respiration. To prevent this critical tissue hypoxia, these

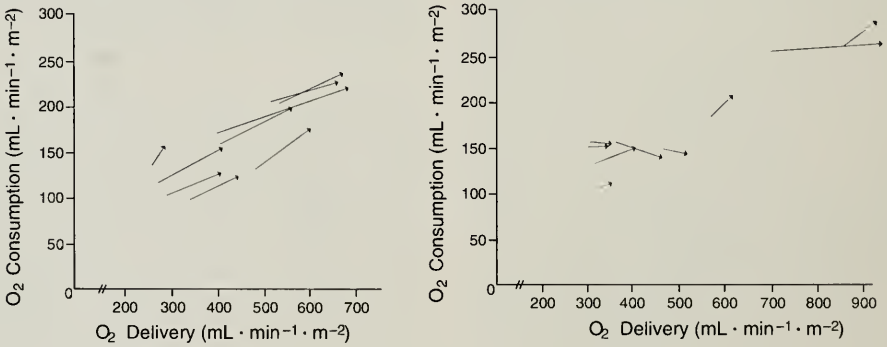

Fig. 16. Changes in oxygen consumption and oxygen delivery induced by dobutamine in 18 patients with ARDS, 9 characterized by increased lactate (left), and 9 by normal lactate (right). (From Reference 49, with permission.)

patients require supranormal levels of D_{O_2}. Mechanisms proposed for the defect in oxygen utilization are

1. peripheral arterial-venous shunting of blood, bypassing tissue capillary beds—this would result in a failure of extraction and subsequently high venous oxygen saturation in the setting of lactic acidosis.

2. histotoxic injury—data regarding this are confusing, with some investigators demonstrating impaired ATP regeneration in septic shock, whereas others have found normal ATP concentrations.[50]

3. diffuse capillary leak syndrome—may lead to impaired extraction of oxygen due to edema in peripheral tissues. This leads to a decrease in the effective capillary density, which is compounded by the increased oxygen demand of inflammatory cells.

These data suggest that whatever the mechanism, peripheral defects in oxygen utilization may be overcome by increasing tissue perfusion and raising systemic D_{O_2}.

In all of the above-mentioned studies, $\dot{V}_{O_2}$ and D_{O_2} were calculated via the indirect Fick method. In this calculation, the same measurement of C.O. is used to calculate both D_{O_2} and $\dot{V}_{O_2}$. If a measured variable is used in the calculation of two derived parameters, error in measurement couples the calculated parameters and introduces a bias, which can lead to incorrect conclusions. Archie[51] has suggested that this common error can lead to the conclusion that there is a relationship when, in fact, none exists. Others, however, have shown that the D_{O_2}-$\dot{V}_{O_2}$ relationship observed is influenced to a negligible extent by shared error.[40,52,53] To avoid this methodologic error from mathematical coupling, it has been suggested that $\dot{V}_{O_2}$ be measured independently from D_{O_2}. To achieve this, $\dot{V}_{O_2}$ can be determined by analysis of respiratory gases, whereas D_{O_2} can be calculated as the product of thermodilution CI and C_{aO_2}.

Using the direct method to calculate $\dot{V}_{O_2}$ and the indirect Fick method to calculate D_{O_2}, Annat et al[54] showed no correlation between the two methods in eight patients with ARDS. Of note are that, in this study, no patient had an elevated serum lactate and D_{O_2} varied from 15.7 to 18.3 $mL \cdot min^{-1} \cdot kg^{-1}$. Carlile and Gray[55] likewise failed to show supply-dependency in 9 patients with ARDS. Again, however, the mean (SD) differences in D_{O_2} varied only from 517 (176) to 583 (207) $mL \cdot min^{-1} \cdot m^{-2}$. Vermeij et al[56] investigated whether pathologic oxygen supply-dependency existed in 16 septic and 14 postoperative patients if $\dot{V}_{O_2}$ and D_{O_2} were assessed independently. In septic patients, $\dot{V}_{O_2}$ was 164 (31) $mL \cdot min^{-1} \cdot m^{-2}$ and D_{O_2} was 633 (209) $mL \cdot min^{-1} \cdot m^{-2}$. The slope of the $\dot{V}_{O_2}$-D_{O_2} regression line ranged from –0.10 to 0.08 and was statistically significant in only 2 patients (Fig. 17). In postoperative patients, $\dot{V}_{O_2}$ was 136 (19) $mL \cdot min^{-1} \cdot m^{-2}$ and D_{O_2} was 481 (160) $mL \cdot min^{-1} \cdot m^{-2}$, while the slope ranged from –0.07 to 0.09 and was statistically significant in only 1 patient (Fig. 17). Also, there was no correlation with hyperlacticemia in either patient group. The authors concluded that the lack of a close relationship between independently measured $\dot{V}_{O_2}$ and D_{O_2} could indicate that septic and postoperative patients in stable hemodynamic condition have no pathologic oxygen supply-dependency.

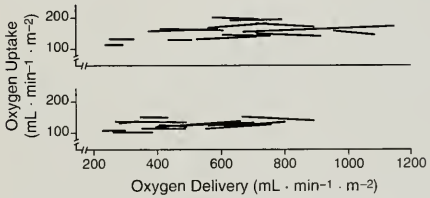

Fig. 17. Relationship between independently measured oxygen consumption and oxygen delivery in septic (top) and postoperative (bottom) patients. (From Reference 56, with permission.)

Ronco et al[57] studied 17 patients with severe ARDS, 10 of whom had elevated plasma lactate concentrations, to determine whether $\dot{V}_{O_2}$ was dependent on D_{O_2}. D_{O_2} in this group of patients was significantly increased from 1,043 (468) to 1,251 (486) mL/min (24%, $p < 0.001$) by blood transfusion. $\dot{V}_{O_2}$, as measured by respiratory gas analysis, did not change significantly after transfusion—ie, 227 (83) to 225 (82) mL/min ($p < 0.38$) (Fig. 18).

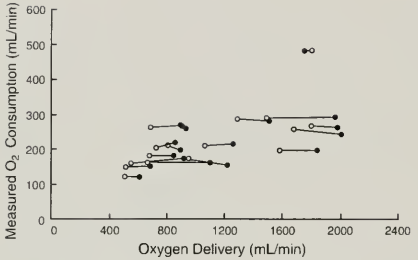

Fig. 18. Individual responses in oxygen consumption to increases in oxygen delivery by blood transfusion. Open symbols (○) denote values determined before transfusion, and closed symbols (●) denote values after transfusion. Oxygen consumption did not change after transfusion ($p > 0.38$). (From Reference 57, with permission.)

In the 10 patients who had elevated plasma lactates and metabolic acidosis, $\dot{V}_{O_2}$ did not increase significantly after transfusion—ie, 224 (100) to 225 (99) mL/min ($p < 0.83$). Of note in this study was that simultaneous determination of $\dot{V}_{O_2}$ calculated from variables shared with the calculation of D_{O_2} yielded a dependent relationship (Fig. 19). The authors concluded that the finding of dependence of calculated $\dot{V}_{O_2}$ on D_{O_2} may be the result of methodologic error.

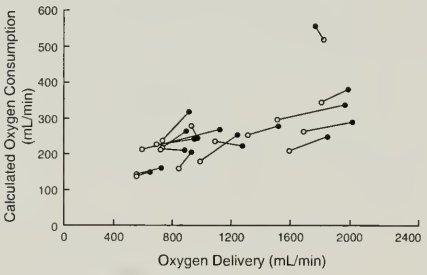

Fig. 19. Individual responses in simultaneously calculated oxygen consumption to increases in oxygen delivery by blood transfusion. Open symbols (○) denote values determined before transfusion, and closed symbols (●) denote values after transfusion. Simultaneously calculated oxygen consumption had an average increase of 31 mL/min ($p < 0.007$). (From Reference 57, with permission.)

In an attempt to help clarify the $\dot{V}_{O_2}$-D_{O_2} relationship, Wysocki et al[58] examined the changes in the oxygen extraction ratio when D_{O_2} was decreased in 12 patients with sepsis during a PEEP trial. In theory, if pathologic supply-dependency exists, the oxygen extraction ratio should be fixed. In this study, $\dot{V}_{O_2}$ was measured by indirect calorimetry to avoid the proposed mathematical coupling bias with D_{O_2}. The oxygen extraction ratio-D_{O_2} relationship was examined, as these two elements do not share common variables such as the CI. The main result of the study was the finding of a zero-order relationship between measured $\dot{V}_{O_2}$ and D_{O_2} when D_{O_2} was decreased from a mean (SD) of 16.2 (4.0) to 11.5 (3.0) $mL \cdot min^{-1} \cdot kg^{-1}$, suggesting oxygen supply-independency of $\dot{V}_{O_2}$. This appeared to be confirmed by a significant increase in the oxygen extraction ratio when D_{O_2} decreased. In contrast, when $\dot{V}_{O_2}$ was calculated via the indirect Fick method, a significant decrease was noted as D_{O_2} was decreased. Also of note was that five patients with hyperlacticemia exhibited the same relationships among oxygen extraction ratio, $\dot{V}_{O_2}$ measured, and D_{O_2} as did the seven patients without hyperlacticemia.[58]

In contrast, Hankeln and colleagues[59] have shown good correlation between the two methods of $\dot{V}_{O_2}$ determination (Table 1). Other studies have shown significant relationships in ARDS patients,[40] and no relationship in non-ARDS patients.[53] These results would argue against the existence of mathematical coupling under most clinical conditions. If there is coupling, it should exist regardless of patient diagnosis or clinical state.

Table 1. Comparative Variables for 25 Patients with Continuous Fiberoptic $S_{\bar{v}O_2}$ Measurements and Noninvasive $\dot{V}_{O_2}$ Measurements*

	Mean ± SEM	No. of Measurements
Noninvasive $\dot{V}_{O_2}$	135 ± 5 mL · min^{-1} · m^{-2}	950
Invasive $\dot{V}_{O_2}$	132 ± 2 mL · min^{-1} · m^{-2}	1,020

*Data from Reference 59. $S_{\bar{v}O_2}$ = mixed venous hemoglobin saturation; $\dot{V}_{O_2}$ = oxygen consumption.

In summary, then, it would appear that pathologic supply-dependency does exist and that augmentation of D_{O_2} benefits the patient. Flow-independent $\dot{V}_{O_2}$ and flow-independent lactate levels should be the goals of augmentation of D_{O_2}. Due to the controversy that surrounds this question, however, one must ask whether elevating systemic

D_{O_2} in critically ill patients does indeed improve outcome.

Should Systemic Oxygen Delivery Be Elevated?

Natanson et al[60] investigated the use of antibiotics and cardiovascular support in a canine model of human septic shock. Purebred beagles were divided into one of the following four treatment groups after surgical implantation of viable *E coli* (30×10^9/kg) intraperitoneally: no therapy (n = 11), broad-spectrum antibiotics (n = 8), cardiovascular support with fluids and dopamine (n = 8), and both antibiotics and cardiovascular support (n = 21). Survival with combined therapy was significantly higher ($p < 0.01$) than survival with either therapy alone or no therapy (Fig. 20). Furthermore, compared with either therapy alone, combined therapy synergistically improved survival ($p < 0.05$). The synergism of the two treatments suggests that cardiovascular support reduces early mortality and extends survival time by improving the early hemodynamic abnormalities, thus giving antibiotics and the host immune system enough time to halt and eradicate infecting organisms.

From the previous discussion, it appears that pathologic supply-dependency in the clinical arena has come to mean flow-dependent $\dot{V}_{O_2}$ in settings where either low C.O. exists or the extraction of oxygen is reduced but adequate flow exists. In the latter condition, aerobic glycolysis occurs, lactate levels increase, and the lactate-pyruvate ratio may increase or stay the same. Although Natanson et al[60] have shown very nicely that in a septic model both antibiotic therapy and cardiovascular support are necessary, the question arises as to whether increasing the D_{O_2} to supranormal levels leads to increases in oxygen utilization, and, if so, whether this has an impact on outcome.

Shoemaker et al[61] calculated the metabolic requirement in a group of surgical patients at risk to develop multiple systems organ failure. They concluded that all such patients develop an initial oxygen debt, and if the debt is not repaid by an increased $\dot{V}_{O_2}$ within the first 24-36 hours, it is associated with a higher incidence of multiple systems organ failure and death. The estimated tissue oxygen debt was calculated from the difference between the actual rate of oxygen consumed ($\dot{V}_{O_{2measured}}$) and the preoperative baseline rate of $\dot{V}_{O_2}$ corrected for anesthesia and temperatur ($\dot{V}_{O_{2baseline}}$ or $\dot{V}_{O_{2need}}$). Thus, the $\dot{V}_{O_2}$ deficit or oxygen debt at any given time is as follows: $\dot{V}_{O_{2deficit}} = \dot{V}_{O_{2measured}} - \dot{V}_{O_{2need}}$. The net cumulative oxygen balance at any time is calculated from the integrated area described by the time-$\dot{V}_{O_2}$ deficit curve. This has been confirmed by a recent study by the same authors[62] in which the cumulative $\dot{V}_{O_2}$ deficit, in 64 patients who died, averaged 33.2 (4.0) L/m^2 at its maximum, 17.8 (2.2) h postoperatively, whereas in 31 survivors with organ failure the cumulative $\dot{V}_{O_2}$ deficit averaged 21.6 (3.7) L/m^2 at its maximum, 10.1 (2.7) h postoperatively; and in 158 survivors without organ failure the maximum cumulative $\dot{V}_{O_2}$ deficit averaged 9.2 (1.3) L/m^2 at 4.1 (0.6) h postoperatively ($p < 0.05$) (Fig. 21). Values for CI, D_{O_2}, and $\dot{V}_{O_2}$ of survivors without organ failure were the highest, values of those who survived

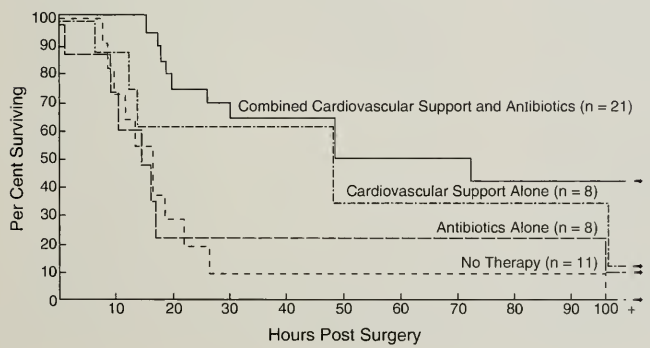

Fig. 20. Percentage of survivors in four treatment groups over time. (From Reference 60, with permission.)

with organ failure were intermediate, and the values of those who subsequently died were lowest but within the "adequate" range (Fig. 22). It follows, therefore, that the relation between increasing D_{O_2} and $\dot{V}_{O_2}$ in patients in whom maximal tissue oxygen extraction is already occurring would identify those patients with an oxygen debt and, presumably, those patients in whom increasing D_{O_2} by whatever means would increase survival.

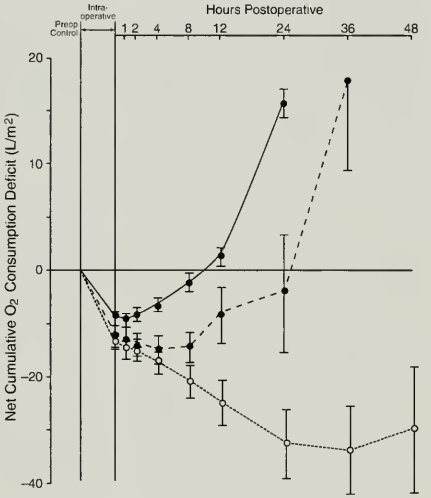

Fig. 21. Net cumulative oxygen consumption deficit for nonsurvivors (dotted line), survivors without organ failure (solid line), and survivors with organ failure (dashed line) calculated for intraoperative period and each successive time period after surgery. (From Reference 62, with permission.)

In separate studies,[63,64] it was demonstrated that a normal $\dot{V}_{O_2}$ may actually be inadequate in critically ill patients in the postoperative period and that a major determinant of outcome was inadequate $\dot{V}_{O_2}$, which led to an oxygen debt and inability to meet metabolic needs. In prospective trials, the outcome in stressed patients in whom therapeutic values were maintained was compared to outcome in stressed patients in whom supranormal values (Table 2) were maintained in the postoperative period.[63] These trials showed that the supranormal group had reduced morbidity, duration of hospitalization, and mortality. In the recent prospective randomized clinical trial mentioned

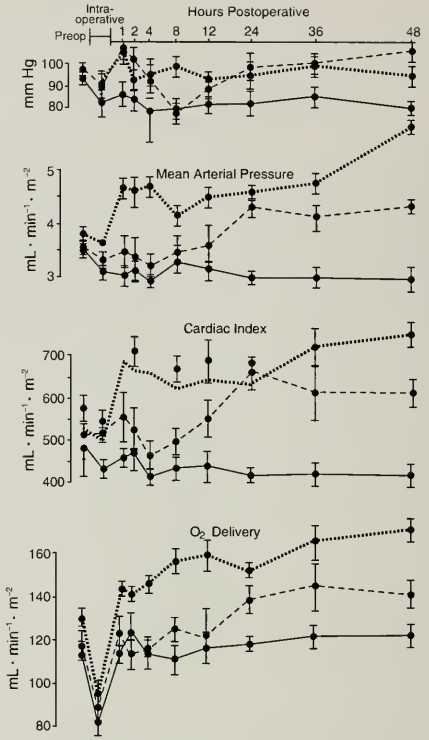

Fig. 22. Serial measurements of mean arterial pressure (MAP), CI, oxygen delivery, and oxygen consumption of surviving and nonsurviving patients during perioperative, intraoperative, and postoperative periods. Nonsurvivors = •—•; survivors without complications = •‥‥•; organ failure = •- -•. (From Reference 62, with permission.)

Table 2. Therapeutic Goals in Critically Ill Patients*

Variable	Goal
Cardiac index (CI)	50% > normal ($4.5\ L \cdot min^{-1} \cdot m^{-2}$)
Oxygen delivery (D_{O_2})	> normal ($> 600\ mL \cdot min^{-1} \cdot m^{-2}$)
Oxygen consumption ($\dot{V}_{O_2}$)	30% > normal ($10\ mL \cdot min^{-1} \cdot m^{-2}$)
Blood volume	500 mL > normal ($3.2\ L \cdot m^{-2}$ in men; $2.8\ L \cdot m^{-2}$ in women)

*Data from Reference 63.

above,[62] a protocol group maintained at supranormal hemodynamic and oxygen transport values had significantly reduced oxygen debt [mean (SD) 7.6 (3.4) versus 17.3 (6.8) L/m^2, $p < 0.05$], fewer organ failures, and a lower mortality (4% versus 33%, $p < 0.05$), compared with a control group maintained at normal hemodynamic values. These data demonstrate a strong relationship between the magnitude and duration of the $\dot{V}_{O_2}$ deficit in the intraoperative and early postoperative period and the subsequent appearance of organ failure and death. An additional three-leg prospective trial by this group[65] compared central venous pressure (CVP) catheter values, pulmonary artery catheter with normal values as goals, and pulmonary artery catheter with optimal (supranormal) values as goals of therapy in high-risk general surgical patients (Table 3). The trial was begun preoperatively and randomized. The results showed no statistically significant difference between the mortality of patients managed with a CVP catheter (23%) and those managed with a pulmonary artery catheter with normal values as therapeutic goals (34%). The use of the pulmonary artery catheter with supranormal values as therapeutic goals led to a significantly reduced mortality (4%) as well as morbidity. The data generated by this group of authors and others are consistent with the concept that forcing patients into a supranormal or optimal pattern by early aggressive therapy reduces oxygen debt and further decreases mortality and morbidity.[62,63,65-67]

Russell et al[68] studied 29 patients with ARDS to determine whether there were differences in D_{O_2}, $\dot{V}_{O_2}$, ventricular function, and multiple systems organ failure between survivors and nonsurvivors. All patients required mechanical ventilation and had a $P_{aO_2} < 75$ torr on an $F_{IO_2} > 0.50$, radiographic

Table 3. Therapeutic Goals for Three Groups*

Variable (Units)	CVP and NR Groups†	PA—Control	PA—Protocol
Similar Goals for Control & Protocol Groups			
Blood pressure (mm Hg)	> 120/80	> 120/80	> 120/80
CVP (cm saline)	> 4 and < 12	> 4 and < 12	< 15
Hematocrit (%)	> 35	> 35	> 34
Urine output (mL/h)	> 30	> 30	> 30
Heart rate (beats/min)	> 60 and < 120	> 60 and < 120	> 60 and < 120
Temperature (°F)	< 102	< 102	< 102
P_{aO_2} (torr)	> 70	> 70	> 70
pH	> 7.3 and < 7.5	> 7.3 and < 7.5	> 7.3 and < 7.5
$P_{\bar{v}O_2}$ (torr)	—	> 40	> 40
PA pressure (mm Hg)	—	> 25/10	> 25/10
P_{pcw} (mm Hg)	—	4-12	< 18
SVR (dyne-s · cm^{-5} · m^{-2})	—	1,800-2,600	> 1450
PVR (dyne-s · cm^{-5} · m^{-2})	—	45-250	45-250
O_2 extraction (%)	—	22-30	22-30
Major Differences in Goals for Control & Protocol Groups			
CI (L · min^{-1} · m^{-2})	—	2.8-3.5	> 4.5
D_{O_2} (mL · min^{-1} · m^{-2})	—	400-550	> 600
$\dot{V}_{O_2}$ (mL · min^{-1} · m^{-2})	—	120-140	> 170

*Adapted from Reference 65. CVP = central venous pressure; PA = pulmonary artery; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; P_{pcw} = pulmonary capillary wedge pressure; CI = cardiac index; D_{O_2} = oxygen delivery; $\dot{V}_{O_2}$ = oxygen consumption.

†CVP group managed with CVP catheter; NR = nonresuscitated group (no central line placed); PA control group managed with PA catheter & normal values as therapeutic goals; PA protocol group managed with PA catheter & supranormal values as goals.

evidence of pulmonary edema, and a pulmonary capillary wedge pressure (P_{pcw}) ≤ 18 mm Hg. No patient had a coexistent myocardial infarction, cardiac valvular disease, or chronic obstructive pulmonary disease (COPD). The 13 survivors had greater D_{O_2} and $\dot{V}_{O_2}$ than did the 16 nonsurvivors, mean (SD) D_{O_2} of 718 (163) versus 491 (219) $mL \cdot min^{-1} \cdot m^{-2}$, and $\dot{V}_{O_2}$ of 183 (50) versus 128 (34) $mL \cdot min^{-1} \cdot m^{-2}$ ($p = 0.004$ and 0.001, respectively) (Fig. 23). There was no difference in the oxygen extraction ratios between the two groups. Multiple systems organ failure developed in no survivors,

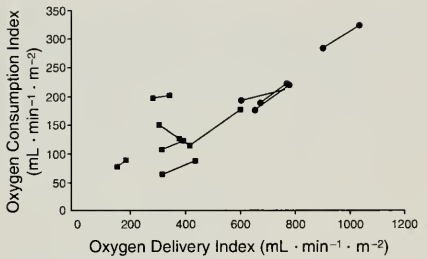

Fig. 23. Oxygen consumption as a function of oxygen delivery before and after acute changes in oxygen delivery in four survivors (●) and six nonsurvivors (■) who had adult respiratory distress syndrome. A significant change ($p = 0.014$) in oxygen consumption was associated with a significant change in oxygen delivery ($p < 0.001$). (From Reference 68, with permission.)

whereas it occurred in 63% of the nonsurvivors. Survivors were also noted to have greater stroke volume and end-diastolic volume indices than did nonsurvivors, despite similar filling pressures. The authors demonstrated a strong inverse relationship between D_{O_2}-$\dot{V}_{O_2}$ and multiple systems organ failure. Of note, there was no compensatory increase in the oxygen extraction ratio of nonsurvivors, suggesting an inability in this group to sufficiently maintain $\dot{V}_{O_2}$ despite 'normal' D_{O_2}. The authors concluded that survivors of ARDS have greater D_{O_2} and $\dot{V}_{O_2}$ than do nonsurvivors and that a peripheral defect in oxygen extraction may contribute to multiple systems organ failure.

Tuchschmidt et al[69] prospectively evaluated the therapeutic benefit of augmenting C.O. and therefore D_{O_2} on mortality in patients with septic shock. Sepsis was defined as a systemic response to infection as characterized by four of the following: temperature > 38.3°C or < 35.5°C, tachycardia (heart rate, HR, > 90 beats/min), tachypnea (respiratory rate, RR, > 20 breaths/min), leukocytosis (white blood count, WBC, > 11,000/mm^3), or delirium. Shock was identified by one of the following: systolic blood pressure (SBP) < 90 mm Hg on two measurements 1 hour apart, intravenous infusion of dopamine for longer than 1 hour to keep SBP > 90 mm Hg, arterial lactate > 3.0 mMol/L. Twenty-five patients were randomized to a normal treatment group (NT) and 26 were randomized to an optimal treatment group (OT). Resuscitation from shock was standardized by use of a printed algorithm. The algorithms for the NT and OT groups were identical except with respect to the end point of resuscitation. The end point of resuscitation in the NT group was a CI of 3.0 $L \cdot min^{-1} \cdot m^{-2}$, whereas in the OT group it was 6.0 $L \cdot min^{-1} \cdot m^{-2}$. The algorithm dictated the use of 5% albumin to achieve a P_{pcw} of ≥ 15 mm Hg. In hypotensive patients with an acceptable P_{pcw}, dopamine infusion was titrated to maintain a SBP > 90 mm Hg. When the P_{pcw} was therapeutic and the SBP was > 90 mm Hg with a CI below the desired goal, dobutamine was infused and titrated to achieve the desired index. All patients were intubated and mechanically ventilated. Patients were transfused to maintain a hemoglobin > 10 g/dL, and S_{aO_2} was kept > 90% with the lowest possible F_{IO_2}. Nutritional support was initiated after hemodynamic stability had been achieved. All patients were treated during their initial 72 hours. In the NT group, CI averaged 3.6 (0.2) $L \cdot min^{-1} \cdot m^{-2}$ mean (SD) and D_{O_2} averaged 8.6 (0.8) $mL \cdot min^{-1} \cdot kg^{-1}$, whereas in the OT group CI was 5.1 (0.2) $L \cdot min^{-1} \cdot m^{-2}$ and D_{O_2} was 12.2 (0.7) $mL \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$). Surviving NT patients stayed a mean (SD) 13.7 (3) days in the ICU versus 7.4 (0.6) days ($p < 0.05$) for the OT patients. D_{O_2} and survival were significantly correlated (Fig. 24). Mortality was 72% in the NT group and 50% in the OT group ($p = 0.14$). It should be noted, however, that because some of the NT patients were spontaneously hyperdynamic and some of the OT patients did not achieve their desired end point, patients were placed in subsets using an arbitrarily determined midpoint of a CI of 4.5 $L \cdot min^{-1} \cdot m^{-2}$. The NT < 4.5 group had a mean (SD) CI of 3.1 (0.2) $L \cdot min^{-1} \cdot m^{-2}$ and a D_{O_2} of 10.9 (1.0) $mL \cdot min^{-1} \cdot kg^{-1}$, whereas the OT > 4.5 group had a mean (SD) CI of 5.7 (0.2) $L \cdot min^{-1} \cdot m^{-2}$ and a D_{O_2} of 13.8 (0.7)

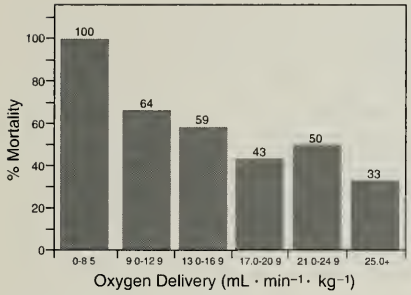

Fig. 24. Hospital mortality rate versus oxygen delivery in all patients. (From Reference 69, with permission.)

$mL \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$). Mortality in the NT < 4.5 group was 74% compared with 40% in the OT > 4.5 group ($p < 0.05$) (Fig. 25). The authors concluded that outcome in patients with septic shock appeared to be related to the level of systemic D_{O_2} and that titration of therapy to increased levels of CI and thus D_{O_2} may be associated with improved survival from septic shock.

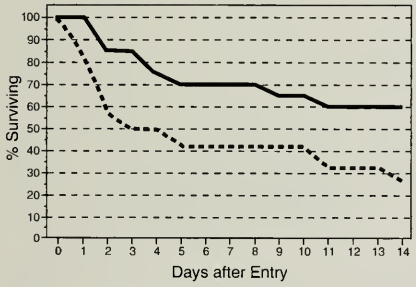

Fig. 25. Survival rate for the normal treatment (NT) group with a cardiac index < 4.5 $L \cdot min^{-1} \cdot m^{-2}$ (——) and optimal treatment (OT) group with a cardiac index > 4.5 $L \cdot min^{-1} \cdot m^{-2}$ (——) over 14 days. (From Reference 69, with permission.)

Experimental studies have demonstrated a relationship between tissue energy deficits and effective organ perfusion.[70,71] A marker of such tissue energy deficits is lactic acidosis. Clinical studies have shown that blood lactate concentrations are frequently elevated when $\dot{V}_{O_2}$ is dependent on D_{O_2} (Fig. 26).[30,72] Thus, clearance of lactic acid levels following resuscitation via increasing D_{O_2} serves as an indicator of restored tissue perfusion. Alouhasna et al[73] have recently observed (1992) that the change in blood lactate concentration in response to therapy designed to augment D_{O_2} can serve as a noninvasive marker of supply-dependency.

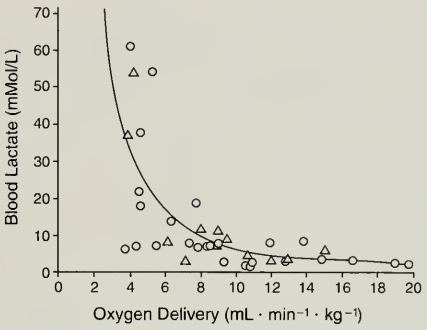

Fig. 26. Oxygen delivery versus blood lactate with power curve ($y = a \times b$, $a = 213.72$, $b = -1.58$) demonstrated ($r = -0.735$, $p < 0.001$). Triangles indicate ARDS, circles indicate non-ARDS. (From Reference 72, with permission.)

Berlauk et al[74] recently tested the hypothesis that optimizing hemodynamics using a pulmonary artery catheter, ie, a preoperative 'tune-up,' would improve outcome in patients undergoing limb-salvage arterial surgery. The tune-up consisted of fluid loading, afterload reduction, and/or inotropic support to achieve predetermined end points. These end points were a P_{pcw} of 8-15 mm Hg, a $CI \geq 2.8\ L \cdot min^{-1} \cdot m^{-2}$, and a systemic vascular resistance (SVR) ≤ 1,100 $dyne \cdot s \cdot cm^{-5}$. The algorithm used to attain these end points is shown in Figure 27. Patients who underwent preoperative optimization of cardiovascular hemodynamics had significantly fewer adverse intraoperative events ($p < 0.05$), less postoperative cardiac morbidity ($p < 0.05$), and less early graft thrombosis ($p < 0.05$) than did the control group. The overall study mortality rate was 3.4%, with mortality rates of 9.5% in the control group and 1.5% in the tune-up group. The authors concluded that in these patients, preoperative cardiac assessment and optimization are associated with improved outcome.

In summary, then, it would appear that the increased metabolic requirements produced by trauma, stress, or sepsis may be limited by inadequate circulatory compensations, including increased CI and D_{O_2}. This is pathologic in the sense that the resultant tissue hypoxia is the major underlying de-

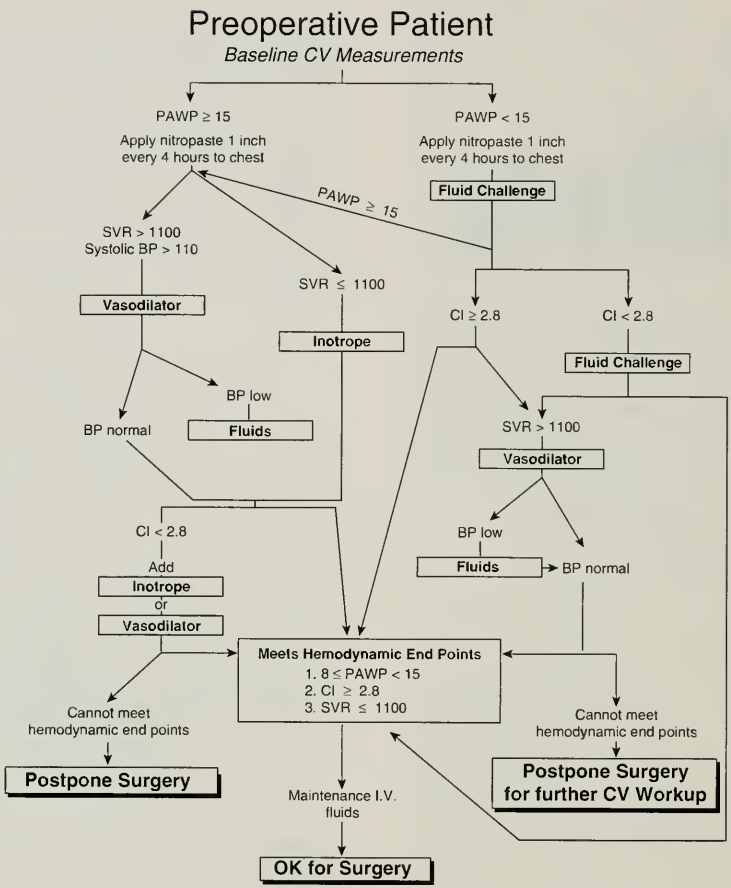

Fig. 27. Algorithm for preoperative cardiovascular tune-up. Cardiovascular measurements were repeated after each intervention. Inotropes = dobutamine or dopamine. Vasodilators = nitroglycerin or nitroprusside. Cardiovascular measurements = pulmonary capillary wedge pressure (P_{pcw}), systemic vascular resistance (SVR), and cardiac index (CI). Measurement units are mm Hg for pressure, dyne · s · cm^{-5} for resistance, and L · min^{-1} · m^{-2} for CI. (From Reference 74, with permission.)

fect of postoperative shock and critical illness; the longer the patient remains critically ill, the more likely that he/she will develop complications. Tissue hypoxia may or may not be associated with an abnormality of extraction (pathologic supply-dependency). It is of the utmost importance, then, that circulatory function be optimized as rapidly as possible, with the end point of resuscitation being flow-independent $\dot{V}_{O_2}$ and flow-independent lactate levels.

How To Augment Oxygen Delivery

1. What is the goal for arterial oxygenation? Normally, 0.3 mL/dL (2%) of arterial oxygen is carried in solution; whereas if 100% oxygen is breathed, this can rise to approximately 2 mL/dL (10%) but hemoglobin is the main carrier. The case for augmenting D_{O_2} by increasing the P_{aO_2} is not answered. Adequate P_{aO_2} could be considered that which is high enough to maintain $\dot{V}_{O_2}$ without the

need for compensatory changes, a reduction in tissue energy levels, or anaerobic metabolism. This varies, depending on the tissue perfused. If the P_{aO_2} drops below 70 torr, the heart is obliged to compensate with an increased coronary blood flow or a decrease in work.[75] When the jugular bulb oxygen tension decreases below 27 torr, the brain becomes a lactate producer; however, the central nervous system can work without increasing blood flow until the saturation is decreased to 85% (P_{aO_2} 50 torr).[75] Accordingly, our current practice is to maintain a hemoglobin saturation > 90%.

2. What is the optimal hemoglobin/hematocrit concentration? The cost of the hematocrit reduction is a lower oxygen-carrying capacity of the blood, which at a given flow decreases D_{O_2}. Heusser et al[76] have noted that anemic newborn lambs have a decreased tolerance to reductions in C.O. and systemic D_{O_2} because their relative anemia provides them with a baseline C.O. and systemic D_{O_2} close to the critical level. Theoretically, the optimal hematocrit range is 40-45% because at this level oxygen delivery is achieved with the minimum of cardiac work. Jan and Chien[77] have shown a reduction in myocardial D_{O_2} when the hematocrit was reduced below 20% or increased above 60%. Similarly, Fan et al[78] and Kuramoto et al[79] suggested that D_{O_2} to the myocardium and to the intestine was changed little by hematocrit manipulation unless hematocrit fell below 30% or exceeded 60%. Cain[23] also noted that $\dot{V}_{O_2}$ did not decrease until the hematocrit dropped below 30%.

In critically ill postoperative patients, a hematocrit of 33% has been reported as being desirable.[80] Current recommendations are to maintain a hemoglobin concentration of 10.0-11.5 g/dL (hematocrit of 30-35%).[75,80] At times, however, transfusion to normal values may be useful. In a study by Fenwick et al,[81] patients with ARDS and lactic acidosis were transfused from a hemoglobin of 9.7 to 12.3 g/dL to increase D_{O_2} from 452 to 585 $mL \cdot min^{-1} \cdot m^{-2}$ ($p < 0.01$). $\dot{V}_{O_2}$ also increased from 117 to 131 $mL \cdot min^{-1} \cdot m^{-2}$ ($p < 0.05$) without a significant increase in CI after transfusion. Thus, the optimal hemoglobin concentration that should be maintained in critically ill patients is unknown.

3. How can cardiac output be augmented? C.O. is the major determinant of D_{O_2} and perfusion. Thus, evaluation should proceed in an orderly fashion, with manipulation of preload first, afterload next, and finally inotropic support. Proceeding in such a fashion limits the increases in myocardial $\dot{V}_{O_2}$.

A useful clinical guide for determining the preload is the P_{pcw}. In hypermetabolic patients, normal filling pressures may not be sufficient to produce increased C.O. Rackow and colleagues[82,83] have shown that the optimal P_{pcw} in patients with septic shock is about 15 mm Hg.

If adequate hemoglobin is present, vascular volume may be augmented with either crystalloid or colloid. Which solution to use remains a point of controversy. Several groups of authors have randomized trauma patients to receive either crystalloid solutions or combination crystalloid-colloid solutions.[84-86] In these studies, no significant improvement in survival or pulmonary function was noted in the groups in which supplemental albumin was given. These authors concluded that from a cost-benefit analysis, crystalloid solutions should be used. In a prospective study of 600 hypotensive patients admitted for trauma, Shoemaker et al[87] noted significant differences in patients resuscitated with crystalloid plus albumin. Patients were noted to have more improved oxygen transport after albumin administration than after crystalloid resuscitation alone despite the fact that the crystalloid group was given a volume two to four times greater than that given the colloid group.

In patients undergoing elective aortic surgery, Virgilio et al[88] randomized the patients to either albumin or crystalloid. The authors found they could maintain P_{pcw}, C.O., and urine output with lactated Ringer's solution given at twice the volume of the colloid resuscitation group, and they recommend crystalloid because of the decreased costs. In another group of patients undergoing elective abdominal aortic surgery, Boutros et al[89] randomized patients to receive either D_5W-albumin, D_5-0.5 normal (0.9%) saline (NS), or 5% dextrose in lactated Ringer's solution (D_5LR). The volume infused was chosen to maintain P_{pcw} as close to baseline as possible. The use of D_5LR postoperatively led to increased pulmonary shunt and an increased alveolar-arterial gradient when compared to the other groups. Also, patients receiving D_5W-albumin diuresed extra fluid at least 24 hours earlier than others. Thus, the authors favored the use of albumin.

Haupt and Rackow[90] prospectively studied 26 patients in circulatory shock (18 septic, 8 hypovolemic) and randomized them to treatment with either 5% albumin, 6% hydroxyethyl starch, or NS. Two to four times more NS, by volume, than albumin or hydroxyethyl starch was required to achieve similar hemodynamic end points. Colloid osmotic pressure was increased by fluid challenge with albumin or hydroxyethyl starch but was markedly decreased by fluid challenge with NS. Resuscitation with NS was found to result in a significantly higher incidence of pulmonary edema than did resuscitation with albumin or hydroxyethyl starch. Urine output was not different among the groups. The authors concluded that 6% hydroxyethyl starch performed as well as 5% albumin as a resuscitative fluid and that resuscitation with either of the colloids was associated with a lower incidence of pulmonary edema than was resuscitation with NS.

Velanovich[91] performed a meta-analysis of crystalloid versus colloid for fluid resuscitation. He concluded that in trauma patients, crystalloid resuscitation produced a 12.3% difference, with a mortality rate that favored crystalloid, whereas for nontrauma patients a 7.8% difference in favor of colloids was found.

Generally, crystalloid should be administered in a volume two to four times greater than that required for colloid. Shoemaker et al's results indicated that faster resuscitation is the case when colloid is added to the resuscitation protocol.[87] If an interstitial fluid volume deficit is identified, isotonic crystalloid is a reasonable choice. If the patient is hypernatremic from free-water deficit, free-water replacement is indicated. If the patient has an intravascular volume deficit, then colloid replacement may provide the most specific treatment. If, after adequate preload is established, flow-dependent $\dot{V}_{O_2}$ and/or lactate production persists, afterload should be assessed. If the SVR is > 1,100 dyne · s and the patient is not hypotensive, ie, mean arterial pressure is > 65-75 mm Hg, afterload reduction should be undertaken. Therapy should be directed at improving tissue perfusion and oxygenation by dilating metarteriolar-capillary networks to provide more evenly distributed blood flow.[92] Agents currently being used are shown in Table 4. Doses of vasodilators are titrated to decrease the SVR to < 1,100 dyne · s while keeping the mean arterial pressure > 65 mm Hg.

Table 4. Currently Used Vasoactive and Inotropic Agents

Vasodilators
Nitroglycerine
Nitroprusside
Hydralazine
Calcium-channel blockers
ACE inhibitors
Inotropes
Dobutamine
Dopamine (5 to 10 $\mu g \cdot min^{-1} \cdot kg^{-1}$)
Epinephrine
Amrinone
Dopexamine (not available in USA)
Vasopressors
Norepinephrine
Phenylephrine
Dopamine (> 5 $\mu g \cdot min^{-1} \cdot kg^{-1}$)
Methoxamine
Metaraminol

If, after correction of preload and afterload, flow-dependence still exists, inotropic support should be considered. The two most extensively studied inotropic agents are dobutamine and dopamine (Table 4). Dopamine is a naturally occurring catecholamine that acts on dopaminergic, alpha-, and beta-adrenergic receptors, and, as such, its use is associated with an increase in mean arterial pressure, heart rate, mean pulmonary artery pressure, and CI. Dopamine also increases D_{O_2}, but less so than dobutamine.[93] On the other hand, $\dot{V}_{O_2}$ has not been shown to increase significantly with use of dopamine despite increasing D_{O_2}, because the alpha effect of the drug may worsen the abnormal distribution of flow.[93] However, this alpha effect makes this an excellent agent for hypotensive patients.

Dobutamine is a synthetic catecholamine with primarily beta-adrenergic properties. Dobutamine has been shown to increase heart rate, CI, D_{O_2}, $\dot{V}_{O_2}$, mixed venous saturation, and stroke work of the heart.[93] In contrast to the effects with dopamine, mean pulmonary arterial pressure and P_{pcw} are decreased. There appears to be no effect on mean arterial pressure. The decreased pulmonary pressure is consistent with the beta-$_2$ effect (peripheral) as well as the beta-$_1$ effect (cardiac). Thus, $\dot{V}_{O_2}$ is increased secondary to improved tissue perfusion and more evenly distributed flow.[93] Although there has

been concern over increasing myocardial $\dot{V}_{O_2}$. Liang et al[94] have shown that in animal models, the increase in coronary artery blood flow and D_{O_2} to the myocardium are in excess of the increased demand for inotropy. One limitation of the use of catecholamines is tachycardia. In a canine model of endotoxic shock, Preiser et al[95] have shown that administration of alinidine (a specific bradycardic agent) can reverse dobutamine-induced tachycardia and simultaneously improve ventricular function. It is very important to note that hypovolemia must be corrected prior to administration of inotropes or vasodilators, as stimulating the empty heart frequently has adverse effects on systemic and coronary perfusion.

Whatever volume, vasodilator, or inotrope improves $\dot{V}_{O_2}$, that combination should be used vigorously as long as it continues to work and the clinical status improves. If therapy fails, one may consider using vasopressor support in the setting of hypotension. Vasopressors are used last, as they promote lactic acidosis, increase pulmonary shunt, and increase pulmonary arterial and capillary pressures. This is probably related to the fact that the 'shunt' circuits are not vasoreactive and hence these agents do not directly affect the abnormal vessels but at the same time do constrict normal capillary beds (Table 4).[96] Vasopressors are useful, however, for increasing mean arterial blood pressure, and thus they help to maintain coronary and cerebral blood flow.

Summary

In conclusion, it appears valid to apply the concept of oxygen transport in the management of critically ill patients. It should be recognized that there are potential errors in measurement of D_{O_2} and $\dot{V}_{O_2}$, most notably when $\dot{V}_{O_2}$ is measured by the indirect Fick method.

When applied in the clinical setting, supply-dependency is frequently interpreted as flow-dependent $\dot{V}_{O_2}$, with or without an abnormality of extraction. The pathologic component usually refers to the effects of tissue hypoxia and not necessarily to abnormalities in extraction ratio and a consideration of critical points. In addition, the presence of aerobic glycolysis has not been utilized in the evaluation of the plasma lactate values.

The diagnosis of inadequate D_{O_2} is made when flow-dependent $\dot{V}_{O_2}$ and/or flow-dependent lactate levels exist. When either of these situations exists, an oxygen 'challenge' should be considered, ie, increase D_{O_2} via fluid loading or inotropic support.[97] If $\dot{V}_{O_2}$ significantly increases when D_{O_2} is increased, clinical supply-dependency exists and D_{O_2} should be maintained at a higher level.

To increase D_{O_2}, the following guidelines have been suggested:[97]

1. Hypoxemia should be corrected by airway control, adjustment of F_{IO_2}, and mechanical ventilation, if necessary, to maintain a hemoglobin saturation $\geq 90\%$.

2. In the presence of anemia or hemorrhage, transfuse blood to maintain a hematocrit of 30-35%.

3. The next step is volume-loading with crystalloid or colloid solutions to maintain a P_{pcw} of approximately 15 mm Hg. Note that the optimal wedge pressure should be assessed on the basis of fluid challenges, with serial measurements of filling pressures and cardiac indices.

4. If, after the above steps have been performed, the low D_{O_2} is felt to be secondary to inadequate C.O., inotropic support should be given. The agent of choice at this time is dobutamine. The most common cause of a lack of response to dobutamine or an adverse reaction is inadequate volume-loading.

5. If a vasopressor is required, dopamine is a good first choice, but norepinephrine can also be used in more severe cases.

6. The other vasoactive agents (dopexamine, amrinone) may be appropriate as adjuncts rather than primary treatment.

More research is necessary in the clinical setting to both define and evaluate "pathologic" supply-dependency and its impact on individual organ function and whole-body physiology and metabolism. Much of this research will require new tech-

nologies of measuring whole-body and organ-specific physiology and metabolism.

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Cerra Discussion

Wood: In the previous presentation, I discussed the treatment of pulmonary edema, and you just discussed treating the inflammatory state. One of the reasons why people get confused about the apparent discordance between these approaches is they don't do what you invited us to do, which is to distinguish between the two different problems that we're treating. Too often, because there is an overlap between sepsis syndrome and ARDS, we pretend that we're using the same treatment goals for both conditions. In the patient that I presented with early ARDS and later septic shock, the early goals were to treat the edema with the lowest wedge pressure giving adequate D_{O_2}, and later goals were to treat the "something else," in this case septic shock, by ensuring an increased wedge pressure and output. That's a comment that I wanted to get out in case anybody else sees it that way. I think that we get ourselves into artificial battles when we're not specific about what we're treating. I presented the canine and clinical data relating survivorship in ARDS to negative fluid balance in the inflammatory state of septic shock. There are, now, growing data, the Tuchschmidt data,[1] that you (Cerra) put up on a slide as another piece of evidence that having a higher cardiac output confers better outcome on patients with septic shock. That paper implies that those poor patients who fell into the "no treatment" group whose cardiac index was left at the high normal value of 4 L/m^2 were unfortunate. They should have had a higher cardiac output like the "optimal treatment" group whose cardiac index was increased to 5 $L \cdot min^{-1} \cdot m^{-2}$, yet there was no significant difference in survivorship between the 2 groups ($p = 0.14$). A retrospective analysis disregarding the groups into which patients were randomized showed a correlation between survivorship and D_{O_2}, which I interpret to mean that if patients' output can be raised with industrial doses of dobutamine (30 $\mu g \cdot min^{-1} \cdot kg^{-1}$), they have a better chance of survival.[1] This is hardly cause-effect! Does that have anything to do with oxygen delivery?

1. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992; 102:216-220.

Cerra: Oh, I think absolutely, and I think he showed it in this study.

Wood: You mean the oxygen delivery went up, and survivorship went up? Not between the randomized groups did survivorship differ.[1] And when D_{O_2} was increased in the "optimal treatment" group, O_2 consumption did not increase.[1]

1. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992; 102:216-220.

Cerra: Let me go back and just refocus this. He (Tuchschmidt) fixed content and manipulated delivery.

Wood: Delivery of what?

Cerra: Oxygen. D_{O_2}.

Wood: Well, it seems to me there are lots of things that go up when the cardiac output goes up. One of them is oxygen, and one of the cruxes of the matter that we're trying to get at here is whether the oxygen has anything to do with it. Even if I interpret that data as being association between increased oxygen delivery and survivorship, the fact that O_2 consumption did not increase with D_{O_2} suggests that any benefit was not due to correcting anaerobic metabolism. On the other hand, I'm not so sure that a benefit, if and when it is demonstrated, wouldn't be due to the increased blood flow washing out the metabolites, delivering the appropriate nutrients, or doing any number of other things to the inflammatory response, which in the final analysis isn't oxygen. I'm asking, now.

Cerra: You won't get an argument from me on that question. I think it's an appropriate question to ask. Why do I say that? Let's say the following: An individual cell, such as the liver cell, is now being driven by inflammatory mediators into an active state of acute-phase protein synthesis. If you now drive it and you don't give the nutrient to it, it'll cannibalize itself as oxidative substrate and as substrate for protein synthesis. In a clinical study, Giovannini and his group looked at oxygen delivery and extraction ratio, and they used amino acid loading as a dependent variable. They found $\dot{V}_{O_2}$ and extraction ratio to be dependent on amino acid supply. I find it terribly provocative, in light of what you're asking. I don't know the answer. If I would rephrase your question, the question would be, "Is oxygen delivery a surrogate marker for something else?" And I don't have any data—I can only give you an opinion. My opinion is that I think it's

both. I think it's quite possible that once oxygen delivery has been satisfied, some other nutrient(s) may become limiting and require an increase in supply.

Wood: So that's the crux of a lot of the discussion here, in terms of oxygenation failure at a cell level: Is this oxygenation failure? And when $\dot{V}_{O_2}$ does not increase with D_{O_2}, and increased D_{O_2} didn't fix the lactic acidosis, and the survivor/nonsurvivor ratio does not change when D_{O_2} is prospectively increased, neither supply-dependence of O_2 consumption nor lactic acidosis gave Tuchschmidt and his group any marker or indicator that anerobic metabolism is important in septic patients after they receive conventional resuscitation.

Cerra: It stayed the same.

Wood: That's right. So it's something else happening, and yet the largest number of people that I've talked to about this think that the issue is increasing the delivery of oxygen to fix anaerobic metabolism. I think everything you said here questions that. It's not necessarily delivering oxygen to fix anaerobic metabolism, for the lactic acidosis of septic shock is due in part to accelerated aerobic glycolysis.[1,2]

1. Curtis SE, Cain SM. Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic endotoxin-treated dogs. Am Rev Respir Dis 1992;145(2, Part 1): 348-354.
2. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. Am J Physiol 1991;260(5, Part 1):E669-E774.

Cerra: Well, I don't make that interpretation of the data. I think the data say that as long as you're on the supply side, you've got an anaerobic condition in the cell that correlates very strongly with the subsequent development of organ failure.

Wood: But you don't think most septic patients are on the supply-dependent side of O_2 consumption?

Cerra: Once you have them over the supply-dependency, the patients will go on to develop organ failure many days later irrespective of maintaining oxygen transport. Progressive organ failure probably involves other mechanisms of cell regulation, some of which may have been influenced by ischemia-reperfusion. Saying it another way, I think we have to move out to what's going on in the cell. Perhaps define a delivery/distribution function for perfusion that applies to the microcirculation of an organ, and get on into the business of looking at the metabolic derangements that probably lead to the organ failure syndrome.

Dantzker: Well, as usual, Frank (Cerra), your presentations are daunting. But I think the most important thing you said, to me, is that you have to really define the patient population because, clearly, we deal with different groups of patients, and I'm not certain that patients I see in the ICU necessarily all fit so carefully into your scheme of multiple organ failure.

Cerra: I agree.

Dantzker: My patients clearly have not been analyzed to the same degree of intensity as have yours. I think that maybe we all have to stop thinking in these very simplistic terms of measurements of global variables and start looking at specific cellular function, which is clearly the direction. You pointed out something that I would have had I been here the other day, and that is, mainly, that a lot of the argument about supply-independence and dependence and mathematical coupling begins to break down a little bit when you look at data like Haupt's or Bihari's,[1,2] where, in fact, in patients studied the same way, with similar ranges of changes in oxygen transport, one group appears to be dependent and one group doesn't. It makes me a little uncomfortable ascribing it all to mathematical coupling. Finally, I have one other problem. That is, I can't achieve these kinds of tremendous increases of oxygen transport that you speak about. We've tried it. Other people have reported in the literature. We get maybe, if we're lucky, a 40% increase in oxygen transport, which, maybe, gives you a 10 to 15% improvement in oxygen consumption. Those seem to me to be very small numbers. I don't know how Tuchschmidt got all his patients up to cardiac indices of 5.5 to 6.[3] Do you think that 10-15% improvement in oxygen consumption is clinically significant?

1. Haupt MT, Gilbert EM, Carlson RW. Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis 1985; 131:912-916.
2. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 1987;317:397-403.
3. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992; 102:216-220.

Cerra: My answer is yes, because you're dealing with 1-2 torr at the level of the mitochondria, but I think you're asking the same question that Larry (Wood) is. Let me see if I can phrase it, "How much of this so-called supranormal flow is for the delivery of oxygen and how much is for other nutrient supply?" I don't know the answer to that, and it's an exceedingly difficult question to try to answer in a clinical model.

Dantzker: But also I think how much of it is due to alterations in the microvascular circulation? All of

these things are done with drugs. One could argue that really what you did was similar to what Bihari did,[1] which was to alter the microvascular circulation. I feel strongly that what we're really talking about is O_2 transport and not O_2 delivery. I want to make that point tomorrow. We measured D_{O_2}, we're talking about a transport phenomenon, we're not talking about delivery. We have no idea what's being delivered to the tissues.

1. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 1987;317:397-403.

Cerra: I accept that and would make one other point, and then get back to Dr Morris's question. I think the advantages of this sort of classified approach in a small group of patients are two. One, it gives you some very clear hypotheses to test; so, you begin to clear the water, in terms of what are relevant questions and what aren't. Number 2, which is a corollary of that, you can now define two categories of outcome variables that are useful. One category is disease-related outcome variables: Do you change the shunt fraction? Do you change the saturations? In some of the nutrient pharmacology studies, we looked at in-vitro tests of immune function. Those are disease-related outcomes. The second advantage is that you can define some relevant patient outcomes, and you can begin to do meaningful outcome studies—for example, length of stay and resource utilization—in addition to mortality. One can begin to define continuous and categorical variables and stratify risk—points that Dr Morris is probably going to address.

Morris: I just have a brief comment and a suggestion that may be useful clinically to try to separate increased cardiac output effects from an increase in oxygen transport, and it seems to me that that's conceptually a relatively straightforward issue to deal with prospectively. You could, if you're keeping one group at a hemoglobin of 10-11 grams %, and if we don't know what the best hemoglobin level is, there's no reason not to seriously consider configuring oxygen transport increase through hemoglobin increases in one group, as opposed to flow increases in another, and keep everything else identical. Although that may sound very simple, it's not as simple as it sounds but it's quite manageable.

Hudson: Frank, you made an important point about testing anti-inflammatory agents that I think I should have made in my talk. I want to amplify a little bit on what you said. I've been concerned, in talking to some of the companies planning to study some of these agents, about the rush to apply these agents in clinical studies with inadequate preliminary information about the biological effects, and without knowing enough about the dose, the route of the administration, the distribution, and the pharmacodynamics to know that the agent actually can counteract the putative mechanisms that they're supposed to counteract. I think you made the point that we should be looking, if we can and if it's possible, at some biological efficacy of the intent of the agent. Otherwise, I think we'll give these agents in a very expensive study, and we won't find an outcome improvement. We'll say it didn't work, but we really won't know if the patient group was even appropriate to study or whether we gave it the right way.

Cerra: I think you make a terribly important point here, and I'm going to give another little twist to it. I agree exactly with what you're saying. I think we have to treat these multicenter trials as experiments. Why do I say that? Because, to take a simple example, the in-vivo production of a single acute-phase protein by the liver is *never* controlled by one cytokine. Cytokines *never* act in a vacuum: they *never* act alone; they *never* act in the absence of the microcirculatory physiologic environment; and they *never* act in the absence of the sympathetic and parasympathetic tone. Each one of those classes controls metabolic pathways. We, as the people involved in these studies, have to admit we don't understand these cytokine-cytokine interactions. If you look at the gene, for instance, on the promoter of the acute-phase protein B-2-macroglobulin in a rat, there are regions for cortisol, interleukin-6 (IL-6), and a number of other nuclear modulators. It's the mix of those that decides when the gene gets activated. Yes, it's IL-6 dominant—it won't go without IL-6, but that's not the whole story. I think we have to quit being so simplistic in our approach.

Hudson: I agree entirely with the point you just made, and I think that raises another issue. There needs to be some funding other than from industry sources to support these studies (probably a combination in funding). Some of the companies aren't going to want to fund looking at the mechanisms, as you described. Federal funding should support that aspect of the investigations—then we could really learn a lot more about the mechanisms involved in critically ill patients than we currently know.

Wood: David Dantzker asked about the changes in D_{O_2} that are being talked about in the Tuchschmidt paper. It's really interesting to look at the details of the question—whether this is resuscitation or not. The mean cardiac index in those patients is 4 L/min. The mean blood pressure is about 70 mm Hg in the non-treated group, and the mean wedge pressure is 13-15 mm Hg. Ask yourselves whether you could

get that through your IRB—whether to treat those patients. I'm very happy not to treat the patients, the no-treatment group . . ..

Dantzker: What was 3, index of 3?

Cerra: It's index of 3:1, but the pressures were in the 70s.

Dantzker: Oh, well, that's very different.

Wood: This is resuscitation. It is good to resuscitate people from shock, and Tuchschmidt showed it.

Dantzker: I didn't realize they were hypotensive.

Wood: But that's the thing about septic shock—even the ones who had the treatment were still hypotensive. That's septic shock—high cardiac output hypotension is the nature of the beast, but that's how they can increase the cardiac output and, therefore, the D_{O_2}. They've got a lot of systolic reserve after volume resuscitation to wedge pressure of 16 mm Hg, so very large doses of dobutamine could increase cardiac output and D_{O_2} by 25%. Because this increase in D_{O_2} did not reduce supply-side lactic acidosis, or survivorship, all the benefit of resuscitation occurred before the "optimal" treatment. They did the same study in '84[1,2] with septic shock and a separate group with hypovolemic shock. Before treatment, both groups had a very low blood pressure, D_{O_2}, and $\dot{V}_{O_2}$; after resuscitation (with what you would teach your residents about how you treat shock), both D_{O_2} and $\dot{V}_{O_2}$ increased to values approaching those before resuscitation in the Tuchschmidt et al study, where maximizing D_{O_2} conferred no further benefit on $\dot{V}_{O_2}$, lactic acidosis, or survival. Note that our entire discussion is about septic shock and its possible oxygenation failure; there is even less evidence for such pathologic supply-dependence of oxygen consumption in AHRF, where maximizing D_{O_2} also maximizes edema.

1. Kaufman BS, Rackow EC, Falk JL. The relationship between oxygen delivery and consumption during fluid resuscitation of hypovolemic and septic shock. Chest 1984;85:336-340.
2. Schumacker PT, Wood LDH. Limitations of aerobic metabolism in critical illness (editorial). Chest 1984;85:453-454.

Cerra: I'll just make one comment in closing, here, because I think it gets back to a comment Dr Morris made that you're implying and I've implied. One of the ways of viewing his (Tuchschmidt's) data is it shows the limitations of categorical definitions because the logical criticism of his paper is, Why didn't you keep resuscitating the patients until the lactate came to normal?" This is the advantage of operational definitions and algorithms.

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Cost-Benefit Considerations in Managing Oxygenation Failure

Alan H Morris MD

I. Introduction
II. Uncertainty in Management of ARDS
III. Complicated Clinical Problems Require Controlled Studies
IV. Determinants of Intensity of Care and of Patient Outcome
V. Understanding the Process of Medical Care
VI. Protocol, or Decision-Support Tool, Development
VII. Role of the Human Laboratory in Cost-Benefit Evaluation of New Therapy
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> . . . it is still the case that only about 15 percent of all contemporary clinical interventions are supported by objective scientific evidence that they do more good than harm.[1]

Introduction

Cost-benefit considerations include evaluations of primary and secondary costs and of primary and secondary benefits. Costs include not only dollars and dollar equivalents of other resources consumed, but also harm experienced by patients, by families, and by the community as a result of health care decisions. Benefits include primary and secondary positive changes experienced by patients, by families, and by the community. The current crisis in health care delivery is associated with excessive costs. National health care consumes 14% of the national economy. An effective way of reducing costs and simultaneously increasing the quality of health care would be welcome. This could be achieved by a systematic clinical-outcomes-research effort. Most medical care has not been demonstrated to do more good than harm.[2,3] Much of the currently delivered care is likely ineffective and may be harmful. Many past therapies were enthusiastically and widely applied but subsequently withdrawn from medicine when demonstrated to be ineffective or harmful.[4,5] The excessive cost of health care is likely due in part to the unnecessary use of expensive high-technology interventions. The ICU serves as a model of the difficulty experienced by practitioners in distinguishing between useful and useless therapy. The identification and elimination of ineffective but expensive care, unlike many approaches currently being considered, are likely to simultaneously increase health care quality and reduce health care costs.

This paper focuses on the elements that must be in place for patient benefit to be convincingly demonstrated. I only briefly address the cost issue and restrict my comments to the dollar consumption associated with the hospital care of patients with the adult respiratory distress syndrome (ARDS). I discuss the uncertainty surrounding management of ARDS, the need for controlled studies to address complicated clinical problems, the determinants of

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the intensity of care and patient outcome, the need for understanding the process of medical care, the technique for protocol development used at the LDS hospital, and the role of the human laboratory (clinical-outcomes-research laboratory).

Uncertainty in Management of ARDS

The uncertainty concerning the management of patients with ARDS serves as an example of the difficulty of clearly defining benefit. Reported survival for severe ARDS patients varies from 9 to 84%![6-11] Two of the nine original ECMO collaborative trial centers report no significant change in survival of ARDS patients meeting ECMO criteria from 1974 to 1988.[11,12] The survival of such severe ARDS patients treated with mechanical ventilation ranges from 0%[12] to 15%.[11] The 13% average survival is not statistically significantly different[13] from the 1974-77 ECMO clinical trial survival of 9% ($p = 0.15$). Less severely ill ARDS patients also appear to now have the same survival as in the 1970s.[11,14,15] It has been proposed that patients with ARDS are now more severely ill than were those encountered in the past.[16] Nevertheless, the absence of definitive evidence that ARDS mortality has decreased is disappointing considering the many technical advances in ICU care during the past 15-20 years.[17-21] While recent changes in mechanical ventilator management have been associated with increased survival,[6,22-24] these have not been evaluated with controlled clinical trials, and no convincing data suggest that any particular ventilatory support mode is superior for ARDS patients.[25] The lack of standardization of ARDS patient selection, treatment, process of care, and techniques of data acquisition and evaluation makes comparison of many clinical results difficult.[26,27] This precludes a compelling definition of desirable therapy for future patients and denies clinicians the guidance needed to aid them in difficult decisions for complex clinical problems.

A number of promising therapies have not yet proved useful (monoclonal antibodies, prostaglandin inhibitors, corticosteroids, PGE_1, new mechanical ventilation support techniques). The reductionist scientific approach has not yet produced the desired "magic bullet" that favorably alters ARDS patient survival.[28-32] Disturbingly, the majority (85%) of medical therapy has never been documented to produce more good than harm.[2,3] Medical history is replete with therapies initially enthusiastically embraced but subsequently discarded when demonstrated to be ineffective or harmful.[4] The results of the Cardiac Arrhythmia Suppression Trial constitute a compelling recent example.[5] The identification of ineffective therapies through clinical-outcomes research could lead to improvement in the quality of care and to a simultaneous reduction of cost. Current efforts to reduce costs do not appear to include this strategy.

Complicated Clinical Problems Require Controlled Studies

Hundreds of variables can be encountered in the ICU.[33] Unfortunately, humans experience information overload when faced with about 7 variables.[34-36] Results of the application of a computerized protocol suggested that experienced ICU physicians suffered from information overload when faced with only 4 adjustable ventilator variables.[37] Given these indications of human limitation, the need for decision support in the complicated clinical environment becomes more compelling, for both clinical care and clinical experimental purposes.

Holistic (constructionist) clinical-outcomes research in controlled clinical settings provide one means of obtaining meaningful outcome data and thus provide the necessary clinical complement to the reductionist research so prominent in modern medicine. Carefully controlled clinical-outcomes research provides results that may upset carefully thought-out projections based on sound scientific principles. The results of the Cardiac Arrhythmia Suppression Trial provide an illustration of the difficulty thoughtful physicians experience in predicting patient outcome.[5] The death rate of patients who sustained effective suppression of undesirable cardiac arrhythmias after myocardial infarction was, unexpectedly, higher than the death rate of control patients.

The major advantage of an experiment over an observational study is the strength of causal inference it offers. Experimental conclusions are enhanced when based on data with high precision and accuracy. Precision (reliability, consistency) is re-

duced by random error (observer, subject, and instrument variability). Accuracy is reduced by systematic error (observer, subject, and instrument bias). Minimizing associated random and systematic (bias) error in patient samples increases the likelihood of drawing correct inferences for the target population. In group comparison studies, blinding is of value because it reduces differential bias between the groups being compared. The randomized double-blinded trial is the ideal design for a between-group comparison. Except for chance maldistributions, randomization eliminates the effect of prerandomization confounding variables, and double-blinding eliminates the effect of postrandomization confounding variables (unintended co-interventions). Blinding is a design feature as important to accurate causal inference as is randomization. If a study is only single-blinded (better than none) or is not blinded, co-interventions due to observer bias cannot be prevented. Protocols may play an important role in reducing differential observer bias in single-blinded studies or in studies that cannot be blinded.[4,38]

By standardizing therapy, protocols may significantly reduce the random and nonrandom (bias) noise introduced into the clinical environment by clinical care team members. This is especially important in the many pertinent trials that cannot be double-blinded. Protocol control may make interpretation of outcomes-research results easier. Conclusions should therefore be more credible and more likely to lead to action and thus contribute to medical policy formulation.

Determinants of Intensity of Care and of Patient Outcome

Both intensity of care and patient outcome are the products of the interaction of the patient and the clinical caregiver's response (Fig. 1). The clinical caregiver response varies from center to center, from unit to unit, from physician to physician, and even within physicians over time. It is influenced by training (eg, internist vs surgeon), clinical setting (eg, Veteran's Administration vs private hospital), pharmacopoeia (eg, United States vs Germany), available equipment or expertise (eg, nuclear magnetic resonance scanner, 2-dimensional echocardiography, medical specialty availability), financial and community imperatives, experience, and recent exposure to clinical reports and lectures. Recent experiences (including exposure to conferences and publications) may dramatically alter the decisions of physicians from one day to the next. Medical practice vogue or style frequently assumes widespread influence out of proportion to the importance of the initial observations.

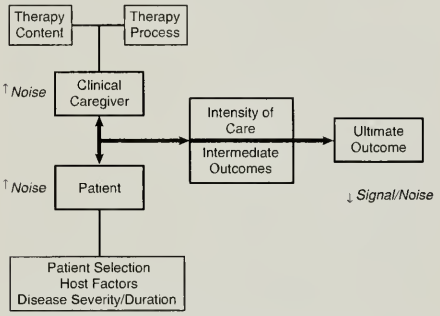

Fig. 1. Major determinants of patient outcome, clinical environment noise, and signal-to-noise ratio for outcome.

Our focus in medicine for both clinical care and clinical research is ultimate patient outcome. The most important ultimate outcome is survival with resumption of a productive life. Unfortunately, the signal-to-noise ratio associated with outcome differences in clinical trials is frequently very low. The noise in the clinical environment is both random and nonrandom (bias). The signal-to-noise ratio for random noise is proportional to the square root of the number of observations (random noise can be reduced by increasing the number of observations or patients in a clinical trial). This is a challenge in critical care medicine. The acquisition of large numbers of patients in clinical trials is not only difficult but costly as well. In contrast, nonrandom or systematic noise (bias), quite common in clinical settings, is not influenced by increasing the number of observations (or patients) and therefore must be reduced by other means.

Both of the major elements that determine the intensity of patient care and the patient outcome (Fig. 1) are sources of random noise and of bias. The patient contributes noise because of uncontrollable host factors and because of disease etiology and severity, extent, and duration of the ill-

ness. Both random noise and bias are included. Local factors influence the disease and clinical problem spectrum. Significant bias is introduced in patient selection, both in clinical care and in clinical trials. The patient identification and selection process is quite imperfect and incorporates much local bias due to the prejudices of individual clinicians and clinical investigators. Characteristics of local clinical environments contribute to the failure of the medical community to establish broadly accepted specific definitions of many diseases. Much work needs to be done.[39,40] The other major element, the clinical caregiver's response to the patient, introduces both random noise and bias. Strong bias is injected into the response of clinical caregivers due to many factors that influence their behavior, including general and local cultural factors, local technical abilities, and experience. These affect the process of therapy, a process that is usually poorly articulated in medical publications. As a result, the reader of medical publications frequently is unable to uncover the rules behind decisions relating to important stages in the delivery of care. For both clinical trials and case reports, this deficiency precludes the definition of "how" the investigation or clinical care is conducted. The reader is usually denied the level of detail necessary for critical review or for duplication of the study.

Understanding the Process of Medical Care[33]

The process of medical care herein means the way we deliver the care provided to the patients. This process is usually not well articulated and, therefore, not easily subjected to detailed control. The content of medical care (what we do or give to patients), the patients selected to receive this care, and the process of medical care (the way we deliver care) are all sources of unwanted noise that obscures the signals we try to extract from patient outcomes. The process of care has received scant attention in clinical medicine. In contrast, much attention has been devoted to process control in another human decision-making environment, the industrial world.[41-43] In industry, control of process has led to a reduction of noise (attainment of statistical stability) and an improvement of outcome. I suspect a similar outcome would occur with process control in medicine. The limited data pertaining to this subject (see below) support this conclusion. Control of process of medical care is currently achieved through decision-support means, such as clinical care guidelines. Most current clinical care guidelines are general, lack specific instructions, and require physician judgment.[44-46] Until recently it was believed that detailed protocol control of critically ill patients was not achievable.[47] It is now clear that workable decision-support tools can be detailed and independent of physician judgment but still include on-line caregiver review of specific instructions (open-loop process control, see Fig. 2 below).[48,49]

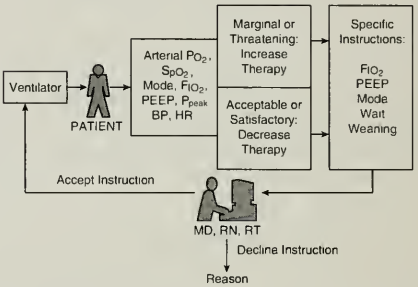

Fig. 2. Schematic of open-loop protocol-controlled management of arterial oxygenation. P_{O_2} = P_{aO_2}; S_{pO_2} = pulse oximetry O_2 saturation; Mode = mechanical ventilation support mode; F_{IO_2} = fractional concentration of inspired oxygen; PEEP = positive end-expiratory pressure; P_{peak} = end-inspiratory peak pressure; BP = blood pressure; HR = heart rate; Wait = time that should pass before the next protocol-determined patient interaction; Weaning = evaluation of the patient for ability to sustain spontaneous ventilation without mechanical ventilation support; Reason = specific, defensible reason for declining a protocol instruction (personal style not a defensible reason); MD = physician; RN = registered nurse; and RT = respiratory therapist.

Control of the process of medical care appears to be beneficial.[50,51] Standardization can avoid vexing problems in very different areas of clinical medicine.[52,53] Computerized protocols have favorable impacts upon hospital pharmacy and infectious disease departments.[54-59] The high survival of control group patients in a recent randomized protocol-controlled clinical trial is encouraging and suggests that such process control may lead to improved patient outcome.[13] Other randomized clinical trials,

using less detailed and manually applied protocols, have demonstrated clearly that protocol-controlled care favorably affects the outcome of patients with thromboembolic disease.[60,61] Pursuit of protocol control of clinical care appears to be a desirable and productive medical research and clinical care aim.

Protocol, or Decision-Support Tool, Development

My colleagues and I have used the following technique to develop protocols that have successfully controlled medical care process. Detailed computerized protocols were developed by an iterative consensus-generation technique to control the intensity of care received by patients enrolled in a randomized clinical trial (Fig. 3).[48]

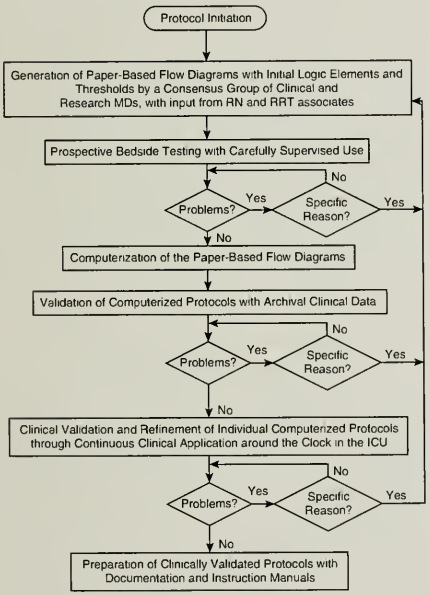
Protocol Initiation
Generation of Paper-Based Flow Diagrams with Initial Logic Elements and Thresholds by a Consensus Group of Clinical and Research MDs, with input from RN and RRT associates
Prospective Bedside Testing with Carefully Supervised Use
Problems?
Yes
No
Specific Reason?
Yes
No
Computerization of the Paper-Based Flow Diagrams
Validation of Computerized Protocols with Archival Clinical Data
Problems?
Yes
No
Specific Reason?
Yes
No
Clinical Validation and Refinement of Individual Computerized Protocols through Continuous Clinical Application around the Clock in the ICU
Problems?
Yes
No
Specific Reason?
Yes
No
Preparation of Clinically Validated Protocols with Documentation and Instruction Manuals

Fig. 3. Diagram of iterative computerized-protocol-generation technique.

Involvement of the clinical staff (physicians, nurses, and respiratory therapists) from the beginning was an important element in the ultimate successful application of computerized protocol control of care. The initial development of logic elements and thresholds was based on a careful review of the literature. Representatives from the Pulmonary, Critical Care, Anesthesiology, and Medical Informatics departments at LDS Hospital participated actively. Around-the-clock bedside testing assured exposure of the protocol to all the vagaries of the clinical environment. The use of the protocol to control clinical decision making throughout the 24-hour day forced attention to details of application that would otherwise have been overlooked. Whenever a protocol instruction was declined by a clinical caregiver, we required articulation of a specific reason. These specific reasons provided the material for iterative review of the protocol elements by the consensus group. This is a critical part of the process. Without such feedback of specific reasons, it would not be possible to refine the protocol and develop a clinically validated and useful product. The key to this part of the process is the willingness of physicians to accept a consensus approach and abandon personal styles of care. The feedback process operates at three levels in the protocol development strategy (Fig. 3). It is an essential tool in the development of the clinically validated protocol that ultimately functions as a set of specific standing orders for the management of mechanical ventilation for ARDS patients. The consensus approach generated a protocol based on published data and extensive review by a panel of experts. The protocol constitutes an acceptable, standardized care plan. It is not an exclusive approach, but only one of a number of approaches that might have been adopted.

The computerized decision-support system was used for over 35,000 hours in 111 ARDS patients (survival 67%) and has controlled decision making 95% of the 24-hour day. The survival rate was higher than the expected 31-33% from historical data ($p < 0.05$)[11,15] (Fig. 4). These results have demonstrated that computerized decision support for critical care is feasible. We propose that the development of further protocols would not only increase the level of standardization but also could significantly improve the quality of ICU care.

These protocols successfully controlled management of arterial oxygenation in both patient groups in a recent randomized, controlled clinical trial. The outcomes of 40 ARDS patients after extracorporeal support or mechanical ventilation were

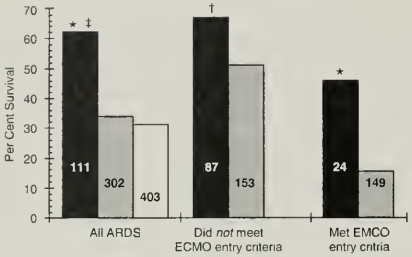

Fig. 4. ARDS patient survival. ■ CPPV protocols at LDS Hospital 1987-1992; ▒ MGH 1978-1988;[11] □ European Collaborative Study 1985-1987:[15] *p < 0.001 vs MGH; †p < 0.05 vs MGH; ‡p < 0.001 vs European Collaborative Study. Numbers within bars indicate total number of patients studied per bar. MGH = Massachusetts General Hospital; ECMO entry criteria = extracorporeal membrane oxygenation entry criteria;[7] CPPV = continuous positive pressure ventilation (volume-controlled ventilation).

compared.[13] The average P_{aO_2} of both treatment groups was 59 torr. These results establish the feasibility of controlling the therapy of arterial oxygenation in severely ill ARDS patients. The unavoidable requirement to interrupt protocol control for diagnostic or treatment procedures, such as radiographs or surgery, did not preclude protocol control of care. The protocols achieved control of an intermediate outcome (P_{aO_2}). The common P_{aO_2} intermediate end point for the arterial oxygenation protocols enhances interpretability of the results because it eliminates the difficult problem of comparing two groups of patients, subjected to different therapies and with different P_{aO_2}. Comparable numbers of changes of oxygen concentration and positive end-expiratory pressure per day were made in patients in these two treatment groups. This suggests that protocol control can not only standardize intermediate outcomes but also can achieve a uniform intensity of care for complicated critically ill patients. The major differences in mode of support did not preclude the achievement of uniform intensity of care.[13,62]

The open-loop-protocol control system for managing arterial oxygenation is illustrated in Figure 2. The outcome of the patients enrolled in the randomized clinical trial for which the protocols were developed was unexpected. Fifteen of the 40 patients (38%) ultimately survived. This 38% survival exceeds the 9-13% expected for ARDS patients meeting ECMO criteria (p = 0.0002). Eight of 19 control patients and 7 of 21 new therapy patients survived. Survival rates in both control therapy (42%) and new therapy (33%) patient groups are not statistically significantly different (p = 0.8).[13]

The 33% survival of our new therapy patients is not statistically significantly different from reported European results following extracorporeal support.[63,64] The 42% survival in our control patients was unexpected and significantly higher than that previously reported for ARDS patients supported with mechanical ventilation. The contribution of protocol control of care to this survival is unknown and as yet unexplored. Because survival of such patients in our hospital was 0-12% from the 1970s to 1985,[12] the intriguing possibility that protocols favorably influenced survival must be considered. Computerized protocols eliminate much intra- and interpersonal medical decision variability. The elimination of unnecessary variation in industrial processes has been an indispensable element in quality improvement.[42,43] Protocols, therefore, may increase medical quality through reduction of unnecessary variation. This is an interesting, though untested, possible explanation for the fourfold increase in survival observed in the control patients.[13]

Role of the Human Laboratory in Cost-Benefit Evaluation of New Therapy

These considerations are underscored by the expense of modern critical care. The average hospital cost for an extracorporeal therapy patient was $97,000, excluding the cost of the extracorporeal system and physician time. The average hospital cost of patients randomized to extracorporeal support exceeded that of control patients randomized to mechanical ventilation by ≥ $19,000.[13] A recent study of ARDS incidence[65,66] leads to an estimate of 10,000-15,000 ARDS patients/year in the U.S. who could be considered candidates for extracorporeal support, if this therapy is widely adopted. This might lead to an increase in cost of ≥ $200,000,000/year nationally, above that of care with mechanical ventilation alone. This great ex-

pense points not only to the need to identify and eliminate ineffective therapies but also to the important balance that must be achieved through cost-benefit analysis.

One approach to the dual problems of inadequate controls in clinical trials[3] and information overload involves a re-examination of the common belief that clinical environments cannot possess laboratory characteristics. Recent results indicate that this does not have to be the case.[10,13,49,58,60] Clinical environments should begin with the delivery of two basic elements: good and ethical clinical care. Adding two characteristics of laboratories to these two basic clinical elements would convert the ICU into a clinical-outcomes-research laboratory (human laboratory). These two laboratory characteristics are reliable data capture and control of therapy. Outcomes-research laboratories would be sites of delivery of good and ethical care under conditions that would permit the conduct of more credible investigation than is currently possible. These laboratories could be the sites of delivery of ICU care that would be more easily defended, from the ethical perspective, than is current ICU practice.[33,67] Because the placebo effect may be responsible for as much as a 75% positive response rate,[4] it is imperative that the benefits of high-technology, resource-intensive, and frequently invasive ICU care be well documented in controlled clinical trials.

The implication of basing the practice of medicine on the ethical principle of beneficence is that patients benefit from our efforts to help. For the physician to be confident that patient benefit will follow an intervention, specific outcome information is required. This outcome information is frequently unavailable. In addition, the physician who attempts to integrate knowledge from the pertinent literature with all patient data, including results of the physical examination, frequently faces a nearly impossible task because of the problem of information overload. Interestingly, many of us still accept this inhuman challenge of obtaining "all the information," including laboratory, historical, physical examination, special study, and x-ray, to mentally process it to yield the "right decision" for the patient. This traditional approach seems incompatible with our intellectual limitations.[33-35,67] In practice, the medical community often invokes another definition of beneficence, the intent to do good. Without definitive information, physicians try to do good and do the best they can. It is of interest to note that while the intention of the medical community to do good is accepted as an ethically sound basis for much of the care we deliver, in other realms of human endeavor we do not accept intentions as proper justification for action ("the road to hell is paved with good intentions").

Summary

The evaluation of new therapy poses a formidable challenge in intensive care medicine. When therapy evaluation cannot be double-blinded, as in the evaluation of extracorporeal support, the problem becomes more difficult. The result of the extracorporeal clinical trial, like that of the ECMO trial in the 1970s, is a potent reminder of the importance of concurrent controls in such evaluations. We should view with caution ethical objections to controlled trials of therapies that are not supported by credible data. A stronger ethical argument may frequently be mounted in favor of a randomized, controlled clinical trial. This is particularly pertinent in the high-technology ICU environment in which information overload is intense. The establishment of ICU human laboratories should enable the medical community to make much needed progress and help us identify the useful elements in our therapeutic armamentarium.

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Morris Discussion

Mathews: Thank you for pointing out that the reader is often unable to uncover the rules behind patient management decisions. Also, in some of the reading that I've done in preparation for this, I saw many definitions for the same things, using many different symbols and many different phrases that were all referring to the same thing. That was very, very confusing.

I was really interested to hear about your computer protocols because I think those are far-reaching and have far-reaching implications—realistic, if not optimal, solutions based on the consensus of experts.

Stoller: Alan, I enjoyed your comments. It brought me back to my fellowship with Alvan Feinstein. I thought I was listening to Alvan. But, if Alvan were here, he would say something regarding the co-maneuvers. You called them "co-interventions." These are synonyms.

Morris: Confounders, right.

Stoller: The concept of uniformity of care presupposes that every maneuver that impacts on outcome is controlled. Now, in dealing with protocols regarding ventilatory strategies and looking at an outcome event that may reflect interventions other than ventilatory care alone, there is no control over other co-maneuvers, like antibiotics, selective digestive tract decontamination, prophylaxis against infection. Some of these other particular strategies may impact on patient outcome but are not part of the protocol that deals with one specific aspect of that patient's care, namely the ventilatory strategy. So, ultimately what one is really talking about is uniform protocols that absolutely standardize the approach to every aspect, to every co-maneuver. This is especially true in a complicated environment and a complicated patient (eg, sepsis with ARDS) where the ventilatory strategy is only one small part of the eventual outcome.

Morris: I agree fully with what you said. We began with oxygenation protocols, because you must remember that these protocols were not generated in order to generate protocols. We would never have dared to do that. It would have seemed like such a foolish endeavor that it would have been rejected out of hand. We developed the protocols in order to have confidence in the results of the actual $ECCO_2R$ trial, and we argued that the biggest driver of therapeutic interventions with regard to ventilator management was, in fact, management of the arterial P_{O_2} in ARDS patients. So, we first developed about 30 pages of those flow diagrams to deal with oxygenation. We have subsequently added ventilation and acid-base control, taking advantage of a number of things that we discussed at this meeting. We intend to develop protocols for hemodynamic management. We will probably begin to start writing those protocols, operating according to the KIS principle (keep it simple). We will probably begin with blood pressure—what we need to do to manage blood pressure, and perhaps deal with urine flow. I want to come back to this issue of simplicity because you've just reminded me of something I'd forgotten to say. We intend to try to embrace the major threads of ICU management—hemodynamic issues, antibiotic issues, fluid electrolyte issues, and so forth. But as you can well imagine, one has to start and build slowly, and just establishing whether it was feasible or not to follow this direction has been a major effort. But we now feel that it's actually feasible. Let me start with the simplicity issue, because I think . . .

East: Before you leave that, Alan, I believe you should point out that at LDS hospital there are also protocols for nutrition, blood products, and antibiotic therapy—so there are a variety of other protocols running . . .

Morris: That's true. Hyperalimentation protocols, for example, have been used for many years. And they're quite interesting. The nutrition protocols are used hospital-wide. They're actually good teaching tools as well; because if the physician orders hyperalimentation, he sees displayed on the screen a set of standing orders. He can change that if he wants; but if he does, and the suggested changes are incompatible with the information in the patient's database, the screen will display a rejection of his changes and bring up the data and the reasons why he can't add calcium to somebody whose calcium is 15, or why you should give potassium to somebody who's got a K^+ of 2.9 and who has just been given furosemide—because all that information is in the

database. That does work in that environment. We also have protocols for antibiotic screening and management. Our institution is interested in more facets than just our oxygenation and ventilation protocols. In the ICU we do intend to include what you have suggested. In fact, we'll take advantage of all algorithms, which is why it was with a bit of selfish intent that I said it sounds as if your scheme for dealing with a number of questions (many of which sounded like they might easily be articulated in dichotomous branching flow-diagrams) could be put down if you just tried. I think what you might find, as we did, is that no matter how hard you try to write down the rules, you find out that they don't work, and that you missed and overlooked some very important things. I'll give you one fascinating example. When we had used the paper-based flow-diagrams for about 7,000 or 8,000 hours at the bedside, with nurses and therapists and doctors following things with their finger, we decided to computerize the protocol. At that point we thought it might work. Right? We gave the job to a programmer, a very bright lady. She programmed it. It didn't work. It made just stupid suggestions. So, we came down glowing with the self-righteousness that goes with the position of knowing what you're doing, and said "That's ridiculous!" I said, "Look. Right here, it says to do this," and, by jingo, she said, "Well that's not what it says at all. I programmed exactly what you have on the paper." We had for about 5,000 hours had a question in the wrong position with regard to command. But everybody knew what the intent was. So every human who looked at it just filled in the gap. It was only in the digital programming that we recognized that we had an error, which if published, would have dramatically misled anybody who wanted to duplicate the work. So, keep it simple. It's very easy to build a simple set of rules and enlarge it if it turns out to be unsatisfactory when we look at its performance. That was the option that we chose: "We'll use P_{O_2}, and if it turns out to be unsatisfactory, then we'll add O_2 content and maybe O_2 content difference, and whatever else is necessary." It's extremely difficult to build a complex protocol with 14 elements, only 3 of which are necessary, and figure out which ones you can eliminate. It's a prodigious undertaking and, in fact, may not even be manageable. So, we think it's very important, in generating a set of rules, to begin with the simplest possible and most constrained database, and make it larger as it proves to be unsatisfactory, rather than the other way around. I mention that because just about every artificial intelligence group of which I'm aware is trying to model the behavior of a very complex problem and very complex work. Many are modeling heart and lung and blood interactions, metabolic rates, and a whole host of things that involve neural networks and very, very complex issues. I do not think it's likely that they will be able to focus upon the elements that appear to be necessary.

Wood: How would you know if the system improved patient care or helped with the teaching?

Morris: Well, those are two questions. How would I know if the system improved patient care or helped with teaching? We did not use the system to improve patient care, so we don't know that yet. We're going to evaluate that if we are able to run a credible trial in Los Angeles at an independent hospital that had nothing to do with the protocol development. We used protocols in all patients, so the protocols remain only as one possibility for the unexpected fourfold survival increase in mechanical ventilation control patients. I have no idea what protocols do. I have no way to explore that other than in a randomized, controlled trial of protocol control, which we are planning now. What about teaching? It's often said that protocols will ruin the teaching program, and several things are mentioned—first, residents learn very effectively from making mistakes. A protocol will teach a resident just to practice by cookbook. Nobody ever mentions, by the way, that years ago when you gave 1.2 million units of penicillin in the hip of a kid with strep, or now amoxicillin, that that's practice by cookbook. It happens to work. It's a pretty effective way to prevent streptococcal sequelae. We do a lot of that in medicine. In fact, whenever we 'know' that something works, we do it, and, in fact, we do it the way it's been documented to work. So, let me respond to that. First, the teaching perspective. It gets in the way. Residents can't "play with the ventilator." They can't adjust, and they can't make mistakes. I'm personally very happy that the pilot who flew the 727 from LA to Puerto Vallarta was trained in a Link trainer, and with an instructor who made actually every effort to protect the pilot from making mistakes during his training. I don't think it would have been particularly useful for the pilot to operate according to the principle we invoke for residents—it's good for them to make mistakes, they learn a lot from their mistakes. Second, I don't believe that residents learn very well from many of the mistakes they make because those mistakes aren't even perceived. And, third, I'm not sure how good a training program we have for residents when 10 different attending physicians taking care of 10 different ARDS patients have 10 different approaches with 10 different justifications. I encountered the same thing, not with ARDS, because I'm old

enough to have trained before ARDS was described (even though we were dealing with it). For diabetic ketoacidosis, one physician gave 100 units of regular insulin I.V., another gave 50; one gave it fast, another gave it slowly; and everybody had his own justification. You know what they told me? We don't tell anybody this, right? It's actually an asset to train in an environment where different people do it differently because you get a chance to see how different people approach the problem, and then you can extract from each of their approaches the best management scheme. I always wondered to myself if these 10 people, with an aggregate experience of 100 person-years taking care of patients, don't know what the best way is to take care of diabetic ketoacidosis, how the hell am I, with 3 months of residency experience, going to be able to pick out the best elements from each of their approaches and synthesize them into something better? I always thought it was a cop-out. They didn't know what to do, and they told me that I was going to find out what to do by watching them not know what to do! I didn't think that was the best training approach. I thought the guy who trained at the Joselin clinic, at which they had a set of rules and a standard approach, at least learned a way that provided a platform for change in the future.

Hudson: Isn't that misleading, though? They thought they knew what was right, and what you were learning in the other system was that it probably doesn't make any difference, or we don't know.

Morris: But let me point out that if we do things by 14 or 20 different methods, and they really don't make any difference, what is the justification for not standardizing? If it makes no difference, and if we're using 14 different techniques with different definitions and different rules, how can we expect to extract any information from outcome data, such as that which is being reviewed by the government when they look at large hospital databases. I agree with you. I think Len Hudson has just said something that's profound—if 10 different reasonable people do it 10 different ways, maybe it really isn't important. Well, if it really isn't important how you do it, why don't we standardize it. In the automobile industry, if there are 10 different ways to put a door in a car, the experience is that you wind up with a car that can't compete with Toyota.

Wood: Can I respond now. A lot of these remarks are for generating discussion and philosophical, and so I don't necessarily agree with what I'm now going to say. [laughter]

Morris: Remember, I have the laser pointer!

Wood: But computers can make a mountain out of a molehill. They can really slow down the process. When you get all of the elements together so that P_{aO_2} is the only thing that you're dealing with in a critically ill patient, then you can, perhaps, make some headway. But getting all the elements together is a complex, integrated process that you demean in talking about the holistic approach, as if the standardized program will really assist this integration. My own sense is that intensive care physicians do a lot of integrating, and the integrating puts together complex processes that you don't believe can be done in more than 4 elements by physicians handling the so-called differential data equations at the bedside of a ventilated patient. Aw, sure they can. I can beat this system, and any of my Fellows that had to take as long as it takes to run through the program to figure out what to do with the P_{O_2} need remedial training. Further, my Fellows' learning objective is to gain independent critical care skills of critical thinking, discriminating instinct, and problem finding—in my view, such learning is facilitated by their being intellectually invested in seeking the solution to each patient problem, and is confounded by mindless following of standardized algorithms.

Morris: Well, our interest in medical care, remember, is maximizing probabilities. I think you brought up some very important issues. When you're taking care of a patient you don't really know what's going to happen to that patient. I don't and you don't. But what we want to do if we have a 27-year-old mother of 2 with ARDS and sepsis is to maximize the probability that the lady will recover. The outcome of that particular lady has really no bearing upon the correctness of the approach or decision. Correct decisions can be followed by poor outcomes, and bad decisions can be followed by good outcomes. But what we want to do is maximize the probability that the lady is likely to recover and return to a productive life. How do we maximize that probability? We must have hard data; we have to be able to define rules and sets that provide information that allow us to address the issue of beneficence, and its corollary, nonmaleficence. Otherwise, we are individualizing therapy, everybody becomes a unique set of circumstances, and it becomes very difficult to generalize the information. Now, that doesn't mean that someone as accomplished as the people in this room could not do a better job, occasionally or even frequently, than a standard program. It also doesn't mean that there aren't a lot of physicians in the medical care community who would do much worse than the standard approach to care. And from the community's perspective, maximizing the benefit of medical care involves looking at, essentially, a cost-benefit assessment for this ap-

proach. One can make arguments for individualization, but I would remind you that individualization is, in fact, what's characteristic of our approach to critically ill patients and ARDS, and what do we have as a result of that? We have wide variability of outcomes reported from different centers with different processes, different and very firmly held opinions about what should or shouldn't be done. The group in St Louis feels very strongly that you should try and minimize lung water and restrict fluids[1] and Shoemaker thinks that just the opposite should be done.[2,3] How can we take that information and generate rules that will allow us to improve the quality of medical care? I think we have to complement what you've proposed. No matter how many good protocols are applied that enhance the probability of good outcomes, there will always be a need for the intelligent physician at the bedside to integrate problems that have been either unanticipated or are newly developed. I mean, protocols for infectious disease developed 20 years ago wouldn't be terribly helpful in the AIDS epidemic. New problems are always going to be present. Remember that decision-support rules don't replace physicians, no more than the computers in the 727 or F-16 cockpits replace the pilots—they *aid* physicians.

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Stoller: I have one comment. If the premise is that a standardized protocol would be better than the average but not as good as the premier group, then normally one of the premises is that this will be widely accepted and embraced. Then one of the concerns has to be that those most in need of the standardized care will be least aware and least likely to embrace the strategies being proposed. So, it becomes this same conundrum—that those people who need to know are least likely to know, or at least one of the concerns is that you must confront as you popularize a standardized algorithm. And, again, this comes from a fairly sympathetic point of view. I agree with the mission. I'm concerned about the ultimate generalizability if effectiveness as opposed to efficacy is the ultimate arbiter of whether this is good or not.

Morris: It is an assumption to assume that protocols either are better or worse than anybody else, including experts. Information concerning expert decision in arenas for which there are no data for decision making (in other words experts taken to the limits of their understanding) demonstrates that those experts are able to predict and deal with problems no better than lay persons. I don't know if that's applicable to expert physicians, but I think that the answers to many of these questions need to await future development. With regard to teaching, which I didn't deal with, I should tell you that it's quite easy, having articulated elements of protocol, to then outline the metarules and the sequence of changes for teaching purposes, and provide residents with much more consistent and referenceable sources of information about how to manage patient problems.

Oxygenation in the Critically Ill Patient: Conference Summary

David R Dantzker MD

The diverse papers presented at this symposium demonstrate the degree to which we have now extended the concept of acute respiratory failure to include abnormal tissue oxygenation as well as hypoxemia.[1-13] The generation of energy, in the form of adenosine triphosphate (ATP), requires that adequate oxygen be transported from the environment to the mitochondria. For a long time we focused all of our attention on the beginning of the transport pathway (ie, oxygenation of the arterial blood). The mechanisms of abnormal pulmonary gas exchange as well as methods of assessing and treating them have been extensively investigated and are now well understood. Our understanding of tissue oxygen exchange, however, is still incomplete. While abnormalities analogous to those seen in the lung are likely to also exist at the level of the tissues (Table 1), we have a long way to go before we will be able to deal with them with the same degree of confidence.

Decreased oxygen transport (T_{O_2}, ie, the product of cardiac output and arterial O_2 content) is probably the most commonly appreciated abnormality of tissue oxygenation because it is easy to conceptualize and simple to measure. (T_{O_2} is often called oxygen delivery, or D_{O_2}, which I believe is a mistake because it may ascribe to T_{O_2} more physiologic importance than it deserves.) Other likely abnormalities are not as simple to evaluate. The diffusion of O_2 across the alveolar-capillary membrane in the lung almost always leads to complete equilibration of alveolar gas with the capillary blood, even in the setting of diffuse lung disease. The resistance to the diffusion of O_2 at the tissue level, by contrast, appears to be considerably greater[14] and in the presence of a systemic inflammatory state it may be markedly increased as cells and fluid fill the interstitial space. Regional heterogeneity of microvascular blood flow may lead to a maldistribution of T_{O_2} with respect to O_2 utilization ($\dot{V}_{O_2}$) so that the tissues that actually require the O_2 may not receive sufficient amounts. Shunting of blood by or through tissues that require it, either on an anatomic or functional basis, is also postulated to have an impact on adequate tissue oxygenation.[15,16]

In order to evaluate the usefulness of various approaches to the treatment of respiratory failure, we need to have valid indices of adequate oxygenation as outcome measurements. While we can debate

Table 1. Abnormalities in Lung and Tissue that Contribute to Respiratory Failure

Lung	Tissue
Abnormal diffusion	Abnormal diffusion
Hypoventilation	Decreased O_2 transport
Ventilation-perfusion inequality	O_2 transport-O_2 utilization inequality
Shunt	Shunt

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A version of this summary was presented by Dr Dantzker at the conclusion of the RESPIRATORY CARE Journal Conference on Oxygenation in the Critically Ill Patient, held in Puerto Vallarta, Mexico, October 8-10, 1992.

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the relative merits and subtleties of calculating the alveolar-arterial O_2 gradient, the alveolar-arterial ratio, the P_{aO_2}-F_{IO_2}, the venous admixture, the strengths and weaknesses of these monitors of arterial oxygenation are straightforward and well discussed in this symposium.[4]

Monitoring the adequacy of tissue oxygenation, as this collection of papers demonstrates, is much more difficult. For all intents and purposes, the tissues remain a black box—with clinicians striving to understand what is going on inside by looking at input and output functions. The monitoring of mixed venous P_{O_2} ($P_{\bar{v}O_2}$) or saturation as an index of tissue oxygenation was a tantalizing possibility, but its limitations, especially in sick patients, are obvious. Even in hypothetical tissue models, the venous drainage approximates tissue P_{O_2} only under ideal circumstances.[17] If metabolic requirements change or tissue capillary density is not optimal or input P_{O_2} is low, the venous P_{O_2} from even an isolated core of tissue is not an adequate indicator of tissue P_{O_2}. If we consider the whole body rather than a hypothetical core of tissue, then the lack of utility of $P_{\bar{v}O_2}$ (a blood-flow-weighted mean value of venous P_{O_2}s from all the tissues in the body) becomes obvious. Even if we did have an index of tissue P_{O_2} or could measure tissue P_{O_2} directly, would it be of much use? Measurements of the tissue P_{O_2} in muscle, for example, have shown normal function with P_{O_2} of 2 to 3 torr.[14] If an adequate value ranges this low, then it cannot be a very sensitive index to follow.

Much has been made of the relationship between T_{O_2} and $\dot{V}_{O_2}$ and the ability of these indices to help us optimize tissue oxygenation. To appreciate the problems with this approach, we need first to look back at definitions. T_{O_2}—the product of cardiac output and arterial O_2 content—provides us with a good estimate of the total amount of O_2 transported by the cardiovascular system and gives us insight into the function of the lungs and heart. However, it tells us nothing about the amount of O_2 actually delivered to the tissues. As an analogy, if you wish to determine how many buses arrive at a given location each day, you don't stand at the exit from the storage garage and count all of the buses leaving. Instead, you stand at the destination and count the buses as they arrive.

$\dot{V}_{O_2}$ is easier to interpret because it mirrors, for the most part, the level of oxidative phosphorylation. However, as we have seen from the paper by Phang and Russell,[3] $\dot{V}_{O_2}$ may be difficult to accurately assess in sick patients, regardless of the method by which it is calculated (ie, from expired gas measurements or by using the Fick equation). Even if we could measure it accurately, the expected $\dot{V}_{O_2}$ for any given clinical situation is unknown. Finally, the $\dot{V}_{O_2}$ is heavily weighted by the metabolic demands of noncritical tissues, like skeletal muscles, and, therefore, may not be a very sensitive index of important visceral function.

The relationship between T_{O_2} and $\dot{V}_{O_2}$ is complex.[18] Under normal physiologic conditions, T_{O_2} is the dependent variable and changes in direct response to alterations in $\dot{V}_{O_2}$. During exercise, for example, T_{O_2} increases progressively in proportion to the level of exercise. This increase in T_{O_2}, by itself, is not sufficient to accommodate all of the increased O_2 demands for energy production, and O_2 extraction (O_2ER) must also increase. O_2ER may reach 80% or even 90% at peak exercise in conditioned athletes. When T_{O_2} is limited, $\dot{V}_{O_2}$ may become the dependent variable. As T_{O_2} is progressively reduced, a critical level of T_{O_2} is reached (T_{O_2crit}), below which any further reduction in T_{O_2} results in a fall in $\dot{V}_{O_2}$. This is generally referred to as the development of supply dependency. In studies of anesthetized animals, T_{O_2crit} is reached at an O_2ER of 50% to 70%.[19,20] In patients and the very few relatively stable individuals who have been studied under conditions of limited T_{O_2}, an O_2ER of more than 35% to 40% is rarely seen, even in situations in which supply dependency appears to be present.[18] This suggests that the ability of the tissues to extract O_2 may differ depending on whether T_{O_2} or $\dot{V}_{O_2}$ is the independent variable. Perhaps this has to do with the specific tissues involved. During exercise, skeletal muscles are the predominant utilizers of energy. Muscle has evolved as an efficient O_2 extractor, as well it must, because it is required to increase its energy production as much as 10 to 15 times the basal level many times during the day. The viscera, by contrast, are not that efficient at extracting O_2, perhaps because they are rarely put in a position of inadequate T_{O_2} relative to their O_2 demands.

A number of authors in this conference have pointed out the difficulty of assessing the presence or absence of supply dependency in humans. In animal studies this is relatively easy. You can vary T_{O_2} over a wide range until you find the point of inflection (ie, the point at which $\dot{V}_{O_2}$ begins to fall in response to further reductions in T_{O_2}). In patients this is not easily done, and a clearly defined $\dot{V}_{O_2}$ plateau (ie, the achievement of supply independency) has rarely been demonstrated. In addition, the $T_{O_{2crit}}$ may vary depending on the manner in which T_{O_2} is manipulated. Increasing T_{O_2} by increasing hemoglobin concentration may have a very different effect on O_2 delivery than increasing cardiac output.

A major problem in evaluating the relationship between T_{O_2} and $\dot{V}_{O_2}$ in the clinical setting is the problem of obtaining accurate data. The calculation of both variables requires the measurement of a number of individual components that are difficult to reliably obtain in critically ill patients. This makes the accuracy of the complex variable somewhat suspect. $\dot{V}_{O_2}$ is a particular problem, whether measured from inspired and expired gas analysis or from the blood side by the Fick equation. While these two measurements should be the same, in patients (especially those on mechanical ventilation) this may not be so. In fact 'noise' in the measurement, due to measurement error and/or physiologic variability, may exceed any real changes expected from a therapeutic maneuver. In addition, as Phang and Russell point out,[3] if the changes in T_{O_2} and $\dot{V}_{O_2}$ are small, we may force a relationship between these two variables due to mathematical coupling that does not really exist.

Because none of these indirect indices of tissue oxygenation is likely to be of much use, we need to look for ways of directly assessing tissue bioenergetics. Experimentally, this can be accomplished by techniques such as magnetic resonance spectroscopy[21] and near-infrared spectroscopy.[22] However, these are not yet ready for clinical use and unfortunately may never be applicable for routine monitoring.

The serum lactate level is commonly measured as an index of anaerobic metabolism, but it is probably less useful than often thought. While lactate levels increase in the setting of tissue hypoxia, excessive glycolysis with a concomitantly elevated serum lactate can also occur in some clinical conditions when oxidative phosphorylation is adequate.[23] Dr Cerra referred to this as aerobic glycolysis. Thus, we would really need to measure excess lactate (ie, the lactate-pyruvate ratio) in order to say anything about the presence or absence of tissue hypoxia. This is much more difficult and not likely to become a routine hospital procedure. In addition, many tissues, especially skeletal muscle, can use lactate as substrate. Thus, lactate produced during regional hypoxia may never accumulate in sufficient amounts to become evident. Other factors such as the acid-base status, the level of catecholamines, and the nutritional state of the patient can also influence the lactate levels independent of the adequacy of tissue oxygenation.[23]

One technique that may become clinically useful as a way to detect inadequate tissue oxygenation is monitoring the development of acidosis in critical tissues. Protons are produced during the hydrolysis of ATP and are reutilized during aerobic production of ATP. When energy is derived primarily from anaerobic sources, the protons accumulate, leading to metabolic acidosis.[24] The recently introduced tonometric measurement of gastrointestinal interstitial pH makes use of this concept and may become a useful and easily monitored clinical index.[25]

The whole concept of monitoring needs to be looked at with a critical eye. In one of the discussion sessions, Dr Wood emphasized the difference between monitoring and measuring. Monitoring a variable has the implication that it will be observed at regular intervals and that we will respond in some well-characterized, systematic approach if the monitored variable falls out of the specified range. Blood pressure, pulse, and ventilator pressures are commonly monitored variables that fit into this category. Many other variables that technology now allows us to observe on an almost continuous basis are not and, more importantly, should not be treated in the same fashion. Many of these measurements inform us that a change in the physiology has occurred but require complex integration with the entire clinical picture before any response can be made. The continuous measurement of mixed venous O_2 saturation is one such example. We must remain aware that just because we have the ability to measure something doesn't

mean that it should be monitored. Sometimes the monitoring of complex variables becomes the standard of care before we have any idea of how to interpret the output. The too-frequent sampling of information, especially if the normal level of variability has not been previously defined, may lead to unnecessary or even unwise interventions.

The proper approach to treatment of patients with respiratory failure requires a clear understanding of pathophysiology of the varying disorders that fit under this general heading. One of the most important points made during this conference was the need to clearly define as homogeneous a population as possible when we test various treatment modalities. For example, a breakthrough in the understanding and treatment of patients with heart failure came with the differentiation of systolic and diastolic cardiac dysfunction. While patients with congestive heart failure often appeared to be clinically similar, their underlying abnormalities were sufficiently different that the optimal approach to therapy also was found to differ. The same thing may well hold for patients with respiratory failure. The abnormalities in patients with ARDS secondary to acid aspiration or viral pneumonia are likely to be different from those in patients with sepsis. A patient with multiple organ failure in the setting of trauma may not have the same pathophysiology as an immunocompromised patient with gram-negative pneumonia. Unless we develop better means of categorizing patients on a pathophysiologic basis, it may be very difficult to develop effective therapy.

We must also discipline ourselves to study any new approach to therapy with carefully controlled clinical trials. The study by Dr Morris and his colleagues of extracorporeal CO_2 removal demonstrates the possible problems of introducing complex new approaches to treatment without careful study.[26] We also have to be prepared to submit our therapeutic approaches to outcomes research because we will be increasingly required to justify the large expenditure of funds directed at the care of critically ill patients.[13]

Finally, in order to remain credible, the medical profession must not allow its agenda to be driven by self-interested third parties. Whether it is new ventilators, monitoring devices, or drugs, we are often faced with the introduction of new technology directed at the patient with respiratory failure before the necessary preclinical steps required to define utility have been taken. Because of the great expense required to develop many of these devices and techniques, there is great temptation to bring them to market before their need is clearly defined or their usefulness verified.

Summary

What then can we say about the present state of knowledge regarding oxygenation in the critically ill patient? We understand the pathophysiology of pulmonary gas exchange and have reasonable clinical tools for monitoring it. We are also usually successful at providing adequate arterial oxygenation, and it is the rare patient who dies of hypoxemia. However, the cost to the lungs of this support—in terms of oxidative injury and trauma—is incompletely understood.

We are beginning to appreciate the complexity of tissue oxygen transfer—enough to realize that enormous gaps in our understanding still exist. We lack a clinically applicable operational definition of hypoxia because we do not yet possess a well-calibrated, easily applied index of tissue bioenergetic function. We have not been able to clearly define the role of hypoxia in the genesis of organ failure, in particular to separate a failure of adequate oxygenation from an abnormality of basic cellular biosynthetic functions.[27] We are not even able, yet, to assure ourselves that increasing TO_2 results in an increase in cellular O_2 delivery or whether increasing O_2 delivery can improve outcome.

There is already a small amount of published data that suggests we are moving in the right direction with regard to answering some of these questions.[25,28] The next few years should provide more answers and allow us to advance the treatment of all forms of respiratory failure.

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Calendar of Events

AARC & AFFILIATES

July 29—AARC Videoconference. The AARC, in conjunction with VHA Satellite Network, presents the fourth of a six-part videoconference series titled "Professor's Rounds in Respiratory Care." The fourth presentation, "Monitoring Oxygenation in the Critically Ill Patient," features Leonard D Hudson MD and David J Pierson MD. Call (214) 830-0061.

August 10-13 in Atlantic Beach, North Carolina. The NCSRC holds its 15th Annual Symposium/Convention, "Professional Challenges," at the Sheraton Hotel. Topics include RC role in organ procurement, political challenges, and current ventilation modes. Contact Debby Harlan at (704) 379-5889.

August 11-13 in Albuquerque, New Mexico. The New Mexico Society for Respiratory Care presents its annual convention at the Albuquerque Convention Center. Highlights include lectures by AARC President Dianne Lewis, Thomas Petty, Robert Kacmarek, and Louise Nett. Contact Schuyler Michael, Pulmonary Rehab, PO Box 26666, Albuquerque NM 87125-6666. (505) 841-1741.

August 15 in Gaithersburg, Maryland. All MD/DC respiratory care practitioners are invited to attend the Respiratory Care Family Day Picnic 1993 at Smokey Glenn Farm. The event is sponsored by MD/DC area vendors. For further information, contact Jeanette Ledbetter at (202) 574-6724 or Elgloria Harrison at (703) 643-9422.

September 22-24 in Frankenmuth, Michigan. The MSRC presents its Annual Fall Conference at the Bavarian Inn Motor Lodge. The Pulmonary Rehabilitation Membership Section opens the conference with a full day of lectures. The following two days feature lectures/workshops in pulmonary and sleep diagnostics. Concurrent lectures are presented on pediatrics, management, gerontology, and adult critical care. Social events include a reception, golf outing, sand volleyball, and an outdoor steak fry. Exhibitors will be on hand to display the latest in technology. Come see Michigan's "Little Bavaria" and enjoy the autumn colors of the Midwest. Contact Caroline Kimmel at (517) 336-7605.

September 22-24 in Lake Kiamesha, New York. The NYSSRC presents its Annual Statewide Educational Symposium at the Concord Resort Hotel. The meeting features management and clinical presentations by John Downs MD, Robert Kirby MD, Roger Mecca MD, Dean Hess MEd RRT, and others. Leisure activities include a golf tournament, barbecue, banquet dinner/show, and private concert by singer/songwriter John Sebastian. The magnificent landscape of the Catskill Mountains, fall foliage, and resort facilities complement the event. Contact Mike Aiello at (914) 795-5300, fax (914) 795-5305.

September 23 in Bettendorf, Iowa. Chapter I of the Illinois Society for Respiratory Care and the Iowa Consortium of Respiratory Care present their fall seminar, "Current Trends in Pulmonary Care," at Jumer's Hotel. Contact Dennis Harker at (319) 383-1387 or Margaret Swanson at (309) 694-5103.

September 23-24 in Napa, California. The CSRC-Chapter 10, the American Lung Association of the Redwood Empire, and the respiratory therapy program at Napa Valley College present the 11th Annual Napa Valley Conference, "Current Concepts in Cardiopulmonary Care." Speakers include Robert Kacmarek PhD RRT, David Pierson MD, and Neil MacIntyre MD. Topics scheduled are "The Respiratory Therapist—Year 2000," nitric oxide, long-term mechanical ventilation, hemodynamic monitoring, update on tuberculosis, and sleep disorders. For information, contact Kate Benscoter at (707) 253-3145.

October 14-16 in San Francisco, California. The Department of Medicine of the University of California-San Francisco School of Medicine presents "Pulmonary & Critical Care Medicine" at the ANA Hotel. Contact Postgraduate Programs, Department of Medicine, 1383 Ninth Ave, Box 0656, University of California, San Francisco CA 94143-0656. (415) 476-5208.

October 15 in Uniondale, New York. The Southeastern Chapter of the NYSRC holds its 25th Annual Symposium, "A Silver Celebration," at the Marriott Hotel. Speakers and topics include Diane Lewis RRT, "The Respiratory Therapist in the Year 2001;" Richard Branson RRT, "Essentials of Mechanical Ventilator Orders" and "The AARC Consensus on Ventilators—Third Generation;" Charles Stolar MD, "ECMO and Neonatal Respiratory Distress;" Alan Fein MD, "Tuberculosis and Its Impact on Health Care Professionals;" and Judith Tietsort RN RRT, "Therapist-Driven Protocols." The symposium features a managers' breakfast, 50 exhibitor booths, the annual awards luncheon, and concludes with a "Silver Anniversary" dinner dance. Contact Edward Schrager RRT at (718) 262-6089.

OTHER MEETINGS

July 21 in Kansas City, Missouri. An interactive full-day workshop, "The Health Professional's Role in Nicotine Dependency Treatment (How to Help Your Patients Stop Smoking)," includes lectures on "Motivating Smokers to Quit," "Evaluating and Treating Nicotine Dependence," and "Developing a Program to Assist Smokers." Contact Mary Cullen CRTT, Pulmonary Rehab Coordinator, Menorah Medical Center, 4949 Rockhill Road, Kansas City MO 64110. (816) 276-8711.

September 30-October 1 in Fresno, California. The Respiratory Care Department and Central Valley Foundation Valley Medical Center holds its 4th Annual Conference, "Controversies in Respiratory Care." Speakers include S David Rubenstein MD, "Liquid Ventilation"; Edward Abraham MD, "Inverse Ratio Ventilation: Effects on the Cardiac System"; Neil MacIntyre MD, "Controlled Hypercapnia"; Alan Horowitz Esq, "Ventilator Alarms and Malpractice"; and William Domonic MD, "Surfactant Therapy for Pulmonary Injuries." For information and a brochure, contact Karen Boswell or Pete Williams at (209) 453-5197.

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept. 11030 Ables Lane, Dallas TX 75229-4593.

New Literary Award for 1993

The American Respiratory Care Foundation is pleased to announce that DeVilbiss Health Care Inc has established an endowment to recognize excellence. The endowment will be used to fund the Dr Allen DeVilbiss Literary Award, which will recognize the "best paper" published in RESPIRATORY CARE, the American Association for Respiratory Care's science journal, from November to October each year. In order to be considered, the paper must address new technology or a new application of current technology in respiratory care.

The award includes $2,000 cash and travel expenses to the AARC Annual Awards Ceremony to receive the award.

Papers are judged automatically. No application is necessary.

* * * * * * * * * *

Other American Respiratory Care Foundation Awards for 1993

1. $2,000 for the best original paper (study, evaluation, or case report) *accepted* for publication from December 1992 through October 1993. This award is *not* limited to papers based on OPEN FORUM presentations.
2. Four awards of $1,000 each for papers *accepted* for publication from November 1992 through October 1993 based on *any* OPEN FORUM presentation (not limited to 1992 OPEN FORUM).
3. Five awards of $500 each for the best papers *submitted* (not necessarily published) by 1993 OPEN FORUM participants who have 'never published' in the Journal. The never-published first author must present the abstract at the Annual Meeting and must submit a paper based on the abstract before the 1993 Annual Meeting (*received* in the Editorial Office by November 1, 1993). Co-authors may have previously published in RESPIRATORY CARE.

Three awards of $333 each are to be awarded to the authors of the three best features from Test Your Radiologic Skill, Blood Gas Corner, Kittredge's Corner, and PFT Corner accepted for publication from November 1992 through October 1993. All three (or none) of the features may be chosen from a specific category (eg, all three may be chosen from Blood Gas Corner).

Annual Meeting Registration Reimbursement

As in the past, any 1993 OPEN FORUM presenter (or co-author designee) will receive complimentary registration for an adequately prepared paper based on his 1993 OPEN FORUM abstract, submitted prior to or at the 1993 Annual Meeting.

All awards will be made at the 1993 Annual Meeting. Papers are judged automatically. No application is necessary.

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BULLETIN

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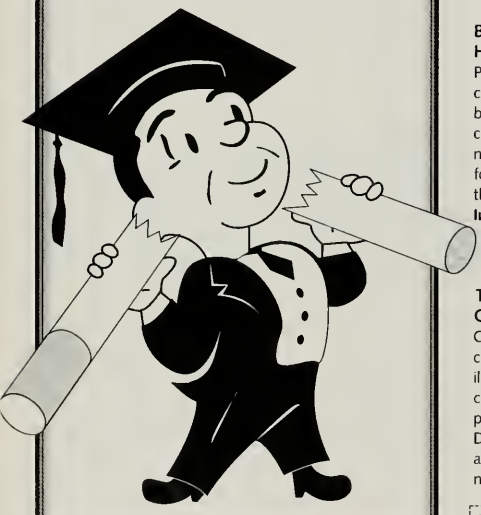

NIK (Nicotine Intervention Kit) —
NIK is a complete do-it-yourself kit for establishing a nicotine dependency intervention program in your health care facility. This kit contains everything you need set up the program. It includes a videotape to introduce the concept to administrators and staff, a business plan to help sell the program to management, a complete set of reproducible forms for use in patient education and counseling, and a list of the latest resources to help inform both patients and staff.
Item R50 — $70 Ea
($50 for AARC Members)

Nicotine Dependency Evaluation and Treatment —
Helps you understand the physiologic effects of nicotine and the tests and questions used to evaluate dependency. Provides an understanding of nicotine, its effects on brain chemistry, its measurement in bodily fluids, and value of self-tests to determine addiction level. Also teaches about nicotine replacement and how to enhance it with behavioral counseling.
Individual Independent Study Package, Item SC1 — $10 Ea

Bedside Counseling of the Hospitalized Smoker —
Prepares you for the role of a smoking cessation counselor to hospital inpatients by teaching assessment and bedside counseling. Help patients cope with nicotine withdrawal, increase motivation for permanent cessation, and understand the factors contributing to relapse.
Individual Independent Study Package, Item SC2 — $10 Ea

Smoking Cessation: Intervention Techniques for the Respiratory Care Practitioner —
Covers four major aspects of smoking cessation — the impact of smoking on illness and mortality, behavioral components, current cessation programs, and effective intervention. Discusses identification of the physically addicted smoker and the effects of nicotine withdrawal. A one hour videotape lecture by Kathleen A. Smalky, MD, MPH.
Item VT35 — $40 Ea, VHS
($35 for AARC Members)

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tem PRB — 10 Extra Activity Books, $12
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($5 for AARC Members)

The Process of Quitting Smoking —
You can help others quit smoking with these tips on how they can start the process.
Item R33 — $10, Pad Of 50
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Item RB — $10, Pkg Of 25
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$101 to $125	8.00	19.00	50.00
$126 to $150	10.00	22.00	60.00
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News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE journal, New Products and Services Dept. 11030 Ables Lane, Dallas TX 75229.

New Products & Services

PORTABLE OXYGEN MONITOR. According to the manufacturer, the OM-100 Portable Oxygen Monitor takes full advantage of its powerful microprocessor—giving you unsurpassed accuracy and alarm operation for rapid diagnostic decisions—and tells you when its batteries and sensors need to be replaced. With SmartMemory™, the OM-100 remembers calibration and all your settings even after being shut down. The OM-100 features long-life reliable sensors, large high-contrast liquid crystal display, automatic verification of proper audible and visual alarm functions, and effortless, error-free calibration. Newport Medical Instruments, Dept RC, 300 N Newport Blvd, Newport Beach CA 92663. (800) 451-3111, (714) 642-3910.

MDI WITH SWIVEL ELBOW AND Y PIECE. IPI Medical Products offers a metered dose inhale with a 360° swivel elbow and Y piece—the elbow adapter allows for the delivery of aerosolized medication directly to the patient, while maintaining the integrity of the circuit. The MDI elbow is available alone or as part of a custom anesthesia ventilator circuit. IPI Medical Products, Dept RC, 3217 N Kilpatrick Ave, Chicago IL 60641. (312) 777-0900; orders only (800) 323-8146 (please mention RESPIRATORY CARE when you call).

CHILD CPR MANIKIN. Resusci Junior can be used to teach and practice all the special CPR techniques recommended for resuscitation of children, to train with ventilation equipment such as pocket masks and manual resuscitators, and to teach water rescue training with the addition of an inexpensive Water Rescue Update Kit. An airway bag (a roll of 30 bags is installed in the abdomen) passes through the manikin torso, over the chest, up through the neck, and out the manikin's mouth—each student uses his own bag and there are no internal manikin parts to clean. Laerdal Medical Corp, Dept RC, PO Box 190, One Labriola Court, Armonk NY 10504-0190. (914) 273-9404.

ENDOTRACHEAL HARNESS. SecureEasy is an endotracheal harness designed for single-patient use that engages a large area of the face (all of the maxilla, from cheek to cheek) and, according to the manufacturer, when tightened down absolutely will not move. Its interface with the tube is a strap that binds the tube into a cradle. At the bottom of the cradle, 10 little stainless steel teeth bite into the tube and hold on "for dear life"—there's no way to dislodge a tube from the SecureEasy unless you do it intentionally—it requires more than 20 pounds of tension to overcome the hook-and-loop fastener on its neck-strap. SecureEasy provides a built-in soft vinyl bite block, as well as an easy-to-use, no-nonsense clamp that keeps the filler tube and valve next to the patient's nose where it's visible. IPI Medical Products, Dept RC, 3217 N Kilpatrick Ave, Chicago IL 60641. (312) 777-0900, orders only 800-323-8146 (please mention RESPIRATORY CARE when you call).

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2 ❑ Hosp 300 to 499 beds
3 ❑ Hosp 200 to 299 beds
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6 ❑ Skilled Nursing Facility
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II. Department
A ❑ Respiratory Therapy
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2 ❑ Pennatal Pediatrics
3 ❑ Critical Care
4 ❑ Clinical Research
5 ❑ Pulmonary Function Lab
6 ❑ Home Care/Rehab
7 ❑ Education
8 ❑ Management
IV. Position
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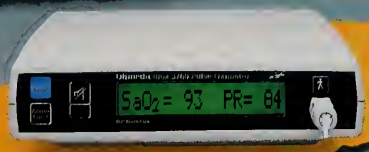

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